Summary

Management of the patient with multiple sclerosis (MS) encompasses a number of distinct, if overlapping, areas. They include anticipation and prevention of problems, symptom control, drug therapies aimed at reducing disease activity and finally, rehabilitation and service delivery.

The recent advent of new immunosuppressant treatments for MS is extremely exciting. Beta-interferons (1a and 1b) are now licensed worldwide and glatiramer acetate (Copaxone®) is in use in the United States. Many more drugs, including intravenous immunoglobulin, mitoxantrone, methotrexate and cladribine, are undergoing trials and some are showing promising results. Future therapies with monoclonal antibodies and adhesion molecules are also undergoing extensive research.

Realistically, however, these new treatments aimed at reducing disease activity will have little impact on existing problems or the degree of disability. Consequently, much of the management of a patient with MS relates to control of the vast array of symptoms. These range from the obvious problems of weakness and spasticity, ataxia and sphincter disturbance, to less common but still important problems such as visual, cognitive, swallowing and respiratory difficulties. Some of the most common, and to the patient most disabling, symptoms are fatigue, thermal sensitivity and pain, areas often neglected by the physician in the face of more obvious physical needs. Much can be done for the patient in all areas. A combination of education, physiotherapy and drug therapy is usually required but occasionally there is a place for more invasive treatments such as intrathecal baclofen administration for severe spasticity or thalamic surgery for cerebellar tremor.

A multidisciplinary team approach is essential in the overall management of the patient with MS,
particularly when assessing their needs as a basis for both inpatient rehabilitation programs and in the provision of a comprehensive community-based service.

**Introduction**

Multiple sclerosis (MS) is an extremely variable disease both within the patient population and within each patient over time. It can affect any area of the central nervous system and therefore produces a multiplicity of symptoms. MS is a disease that strikes young people in the prime of their life and is then present for perhaps 30 or 40 years having little impact on longevity. Prognosis in an individual is unpredictable. Most patients follow an initial course of relapses and remissions but many at some stage develop disease progression and hence accumulating disability.

Management of the MS patient begins at presentation with the first symptom, investigation and subsequent diagnosis. This is a particularly crucial time and the key areas of management are education and support (1). In the established MS patient management can be divided into four main areas: 1) anticipation and prevention of problems, 2) symptomatic treatment, 3) current and future therapies aimed at reducing disease activity and 4) rehabilitation and service delivery.

**Anticipation and Prevention of Problems**

Maintaining good general health is of prime importance. It has been suggested by Petajan and colleagues that regular aerobic exercise increases physical and psychological well-being (2).

The question of whether patients with MS should receive vaccinations has been long debated. Recent work by Miller et al. (3) suggests that the influenza vaccination does not seem to increase the risk of disease exacerbation and thus should not be contraindicated in MS. The risk of other vaccines such as varicella zoster, hepatitis and pneumococcal have not been studied in MS. Theoretically, if molecular mimicry is responsible for disease exacerbation following viral infections, vaccinations of even killed vaccine could activate myelin reactive T-cells. However, the risk-to-benefit ratio of these immunizations is probably low when used in patients at risk and should always be offered (4).

Relapses may be precipitated by intercurrent infections. These should be treated promptly and, more importantly, prevented if possible. This in particular relates to urinary and respiratory tract infections. Large residual urinary volumes or poor intermittent self-catheterization techniques are often responsible for precipitating urinary tract infections. With regular assessments and training these can be avoided. In the respiratory tract early signs of aspiration should be noted and a speech therapist involved early for advice on management.

Spasticity and weakness can also lead to problems with abnormal posture and gait. This can put abnormal strain on the back and result in mechanical problems with considerable pain. Untreated spasticity can also lead to contractures with consequent increasing disability and loss of function.

The importance of recognizing sensory loss should be emphasized, since awareness of this can avoid unnecessary damage to the skin by trauma or burns. Often the skin takes a long time to heal and may even precipitate ulcers which in turn can cause increased spasticity of the limbs. Many of these areas can be covered by the use of a multidisciplinary team approach to follow-up (5).

In the past patients were often advised not to become pregnant as this was associated with disease exacerbation; however, the relationship between pregnancy and MS has become clearer more recently. Retrospective and recent prospective studies have suggested that the relapse rate is decreased during pregnancy but raised during the 3-month puerperium, giving little difference in the overall relapse rate over the pregnancy year or in the long-term disability of the patient. It is generally felt that patients wishing to start a family should not be discouraged from this (6).

**Symptomatic Treatment**

Realistically, the recent advent of new immunosuppressant treatments will have little impact on existing problems and disability. Consequently, much of the management of a patient with MS relates to control of symptoms (7, 8). The range of symptoms in MS is vast, varying from the obvious problems of weakness and spasticity, ataxia and sphincter disturbance, to less common but still important problems such as visual, cognitive, swallowing and respiratory difficulties. Some of the most common, and to the patient most disabling, problems are fatigue, thermal sensitivity and pain, areas often neglected by the physician in the face of more obvious physical needs.

Acute relapses which significantly affect a patient’s function can be treated with a short
course of intravenous steroids, which has been shown to accelerate recovery (9, 10). A short 3-day course avoids the long-term side effects of steroids but care should still be taken prior to initiating therapy to check for the presence of a low-grade urinary tract infection, which if missed can rapidly develop into a serious septicaemia. Blood glucose levels should also be monitored during treatment. Therapy is given as 3 daily infusions of 1 g methylprednisolone in normal saline. Some suggest following this with a short oral course but this is not usually done.

**Spasticity and weakness**

One of the biggest fears of any patient with MS is that of becoming wheelchair bound. Loss of mobility is not only a consequence of weakness and spasticity but can also result from both cerebellar and sensory ataxia. Often, a combination of these factors is responsible.

Spasticity occurs frequently in MS, particularly in the progressive phase of the disease. Although it can be functionally useful in allowing some stability and weight bearing in weak legs, a point which must be remembered before aggressively treating spasticity in ambulant patients (as occasionally this results in loss of function) is that it is usually associated with reduced dexterity, spasms and the risk of developing contractures.

The pathophysiology of spasticity is complex and poorly understood (11). It is often a result of spinal cord damage and tends to affect the lower more than the upper limbs. Spasms are common, painful and can cause problems with transfers. The aims in management of spasticity are to improve function, reduce pain and prevent complications. Therapies can be divided under three main headings: physiotherapy, pharmacology and surgery. In practice it is a combination of physiotherapy and drug treatment which works for most patients. Surgery is a last resort and is usually necessary only if contractures have already formed.

The physiotherapist is extremely useful in educating the patient and helping them to understand and manage their own tone. Posture should be assessed and corrected; normal patterns of movement may need reinforcing and selected movements relearned (12).

There are many pharmacological agents available which reduce spasticity. Most patients can be managed with oral medication but occasionally intrathecal, intramuscular and nerve block therapies are necessary. The most commonly used oral agent is baclofen, a derivative of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Baclofen is absorbed rapidly and has a plasma half-life of 3-4 hours. Its main site of action is thought to be the spinal cord. Baclofen should be started at a low dose of 5 mg b.i.d. and increased slowly until good effect is achieved or adverse effects occur. The usual maximum dose is 20 mg t.i.d. but some patients tolerate up to 40 mg t.i.d. The main side effects are drowsiness, dizziness, mental confusion (particularly in the elderly), weakness and excessive hypotonia. Abrupt withdrawal of the drug should be avoided as hallucinations, anxiety and tachycardia may occur.

Diazepam, clonazepam and the other benzodiazepines enhance the efficiency of GABAergic transmission causing increased presynaptic inhibition of afferent neuronal terminals in the reflex arc. Their sedative and anxiolytic properties are often helpful if they are taken at night to reduce nocturnal spasms.

Dantrolene is different from baclofen and diazepam in its mode of action in that it acts peripherally on skeletal muscle. Reduced amounts of calcium ions are released by the sarcoplasmic reticulum and the force of contraction is attenuated, reducing reflex more than voluntary contractions. The plasma half-life of dantrolene is about 9 h. It should be started at a once-daily dose of 25 mg and increased gradually to a maximum total dose of 400 mg daily. The main adverse event is hepatotoxicity; therefore, liver function should be monitored. Drowsiness and weakness also occur.

Tizanidine is an α-adrenergic antagonist and acts by reducing excitatory transmission in the spinal cord. It has a specific effect on paroxysmal spasms and a positive effect on muscle strength. Hypotension, drowsiness and sedation are its main side effects (6, 13-15). Vigabatrin is also occasionally useful in treating spasticity.

Intrathecal administration of baclofen can be extremely useful in a small group of patients. These are usually nonambulant with severe spasticity not helped by the maximum tolerated dose of oral baclofen (16, 17). As baclofen does not readily cross the blood-brain barrier, administration directly into the subarachnoid space allows direct access to the drug receptor sites in the dorsal horn of the spinal cord and, consequently, much lower doses can be used. The drug is delivered from a pump placed subcutaneously in the abdominal cavity via a catheter which is tunnelled to the sub-
arachnoid space, with the catheter tip lying at T12/L1 (Fig. 1). The pumps are computer programmable allowing for a pattern of differing needs throughout the day and night. However, as the dose can only be altered by a trained programmer, any titration of dose or refilling (every few months) necessitates a visit to a specialized center.

Recently, botulinum toxin type A has been used intramuscularly for severe spasticity (18). This is a neuromuscular blocking agent which acts at the presynaptic terminal by blocking calcium-mediated acetylcholine release. Its duration of action is about 2-3 months after an initial lag of 3-4 days. Botulinum toxin has been used to treat severe spasm causing problems in posture or personal hygiene, such as adductor spasm. The drawback is that large amounts of toxin are needed and it is necessary to repeat the procedure every 3 months. More recently it has been used as a one off treatment in conjunction with splinting and physiotherapy which enables the abnormal pattern of movement to be interrupted and subsequently relearned (12).

Nerve blocks are ideally carried out on purely motor nerves although they are often more effective if carried out proximally when some sensory disturbance may occur. Common sites include the posterior tibial, median, ulnar and obturator nerves. The block is first carried out using a reversible local anesthetic such as bupivacaine, and if appropriate, is repeated using phenol or alcohol. Nerve blocks are usually effective for 2-3 months and can then be repeated if necessary (19).

**Ataxia**
Ataxia is extremely variable, causing only minor problems with finger dexterity in some patients, and a catastrophic loss of upper limb function, mobility and even loss of sitting balance in others. Head titubation may also occur in severe cases and is very distressing for the patient. Ataxia may be one of the worst symptoms and often the hardest to treat successfully.

Physiotherapy and occupational therapy are very important to optimize the patient’s sitting, posture and to supply relevant supportive aids to increase function. Any aids which increase distal support particularly to the upper limbs can help greatly.

Drug therapy is of limited value but occasionally is helpful to some patients. Isoniazid in combination with pyridoxine may have some benefit (20). Other drugs that are often tried to little avail include clonazepam, carbamazepine and propranolol. Recently intravenous ondansetron, a 5-HT3 antagonist, has shown promising results in a small pilot study of patients with severe cerebellar tremor. It was very well tolerated, with the main side effects being headache and constipation (21).

For severe cases it may be appropriate to consider thalamotomy. This is done stereotactically and involves ablating the ventrolateral nucleus of the thalamus. It is beneficial in about 50% of cases but serious side effects can occur, including hemiplegia and dysphagia. Electrostimulation of the same area may be more beneficial and less hazardous, and further research into these techniques is ongoing (22, 23).

**Bladder, bowel and sexual dysfunction**
Most patients with MS will have some bladder disturbance during the course of their disease. Common symptoms are frequency, urgency and nocturia. However, as bladder dysfunction increases problems of incontinence, retention and urinary tract infections can occur (24). Most of these are a result of a combination of detrusor hyperreflexia (causing urgency and incontinence) and sphincter dyssynergia (causing failure to empty and consequent residual volumes). Before treatment is initiated it is important to assess the bladder and in particular the postmicturition residual volume. This
is done by either catheterization or ultrasound (25). If there is no residual volume then detrusor hyperreflexia can be treated with anticholinergic agents (e.g., oxybutynin) beginning with a dose of 2.5 mg b.i.d. and if necessary increasing up to 5 mg t.i.d. The most troublesome side effect is dry mouth which can be severe. If nocturia fails to be controlled with oxybutynin the use of desmopressin (DDAVP) delivered by a nasal spray is particularly helpful (26). DDAVP acts by reducing the volume of urine produced by the kidneys and, therefore, if taken in large quantities or for prolonged periods can result in hyponatremia. Patients must be warned of the potential adverse effects as often they are impressed by its efficacy and wish to take it more regularly. If hyperreflexia is severe and long-lasting the bladder may have very limited storage capacity. This can be increased in some patients with the use of intravesical capsaicin which through its toxic effect on the C-fiber afferents in the bladder wall reduces the drive of the pathological spinal detrusor reflex. The effect of capsaicin in individuals is variable, lasting 1-5 months, and repeat infusions are an option (27).

Detrusor sphincter dyssynergia can be treated using clean, intermittent self-catheterization. Another option, particularly for ambulant patients, is the "Queen Square bladder stimulator". This is a small, portable, hand-held device which vibrates at a frequency of 60 Hz and is applied to the supra-pubic region. It has been shown to facilitate bladder emptying and improve urinary symptoms in patients with neurogenic bladders (28).

Patients often require a combination of therapies but bladder control is usually greatly improved. Occasionally control remains poor and an indwelling catheter should be considered; if this is for long-term treatment, a suprapubic catheter is usually preferred.

Bowel dysfunction is less frequent but probably affects half of the MS population (29, 30). Patients frequently complain of constipation and urgency, while incontinence is less common. Management is more difficult than bladder dysfunction, but the establishment of a routine is important. Often regular treatment with oral agents is enough (lactulose, senna), although glycerine suppositories and microenemas can be extremely useful. Incontinence often associated with urgency can be helped with loperamide (31).

Sexual dysfunction is a problem often overlooked by health professionals but is extremely common in MS (32). Psychosexual counseling should be considered in all cases alone or in combination with other therapies. In men the major complaint is erectile dysfunction. The oral drug yohimbine, an alpha-adrnergic agonist, is effective in some patients. Other drug treatments include intracorporeal papaverine which is usually effective in producing erections. The main side effect is priapism (>4 h) which requires treatment with aspiration of the corpora or intracorporeal metaraminol injections. Injection site reactions can cause hematoma or local fibrotic reactions which may lead to Peyronie-like erection distortions (33). Alfaprostadil (prostaglandin E1) is also given as an intracorporeal injection and has similar side effects as papaverine (34). A new promising orally active drug, sildenafil, is also undergoing trials at present (35). If drug treatments are unhelpful a range of surgical prostheses and mechanical devices are available.

Women complain most frequently of vaginal dryness which can be overcome by the use of lubricating gels. Lack of sensation is unfortunately much more difficult to help.

Visual dysfunction

Poor recovery from optic neuritis or indeed progressive optic neuritis are the most common causes of visual problems in MS, although diplopia, nystagmus and oscillopsia can also be extremely disabling. Patients with optic nerve dysfunction may be helped by referral to low vision clinics. The management of nystagmus and oscillopsia is extremely difficult. Converging prisms may be useful and several drugs have been reported to help in small cohorts of patients, including baclofen, valproic acid, trihexyphenidyl, clonazepam, isoniazid and gabapentin (36-40). Botulinum toxin injections have also been of benefit in severe long-lasting oscillopsia but caution is needed (41).

Cognitive dysfunction

The prevalence of cognitive dysfunction in MS has been reported to be 54-65% in hospital-based studies, but was found to be 40% in a large community-based study (42). The pattern of cognitive decline in MS is predominantly subcortical and the main deficits are in short-term memory, attention, conceptual reasoning and speed of processing. The onset of cognitive decline seems to be unrelated to disease duration or physical disability and little is known about its rate of progression.

Cognitive dysfunction can have a devastating impact on the psychosocial functioning of an MS
patient. Although 50-80% of MS patients are unemployed within 10 years of disease onset, many of them will have a lower than expected level of physical disability to explain this. The same also holds true for the degree of social activities undertaken by patients (43). Identification and assessment of cognitive deficits can help both the patient and the employer. Patients may be candidates for formalized cognitive retraining programs aimed at teaching compensatory mechanisms to aid memory retrieval and sustained attention. Employers once aware of cognitive impairment are able to alter expectations and make adaptations to enable the patient to continue working (44).

Patients with MS may also exhibit psychiatric symptoms. Normally these are mild and include low mood, irritability, poor concentration and anxiety (45). Often medication is not required and patients can be helped greatly by nursing specialists or other disciplines trained in counseling. If antidepressants are required they should be used as in the normal population but with greater attention to possible adverse effects, particularly exacerbation of bladder and sexual dysfunction.

Psychotic illnesses have been described in MS but are infrequent.

Swallowing and speech

Speech problems in multiple sclerosis are usually a result of dysarthria. Although dysphasia does occurs rarely, patients often are able to communicate without any difficulty especially with friends or relatives who have become accustomed to their speech. On rare occasions dysphasia is severe enough to necessitate communication aids, but at all stages the advice of a speech therapist is extremely valuable (46).

Swallowing difficulties may be independent of speech problems and are probably underestimated (47). Many patients will describe fluctuations in their swallow according to factors such as the time of day, temperature and general fatigue. There is great value in an early assessment from a speech therapist to enable education of the patient and caretakers in compensatory mechanisms, such as posture (tucking the chin in or turning the head) or change in diet. They should also be aware of the dangers of aspiration and alerted to watch for this. If swallowing becomes severely compromised a percutaneous gastrostomy should be considered. This is often dreaded by patients and carers alike but actually usually improves quality of life significantly. The patient is still able to take small amounts orally for pleasure but does not have to rely on oral food for nutritional intake.

Fatigue

This is probably the most common symptom in MS and if severe can be extremely disabling, limiting the patient’s employment and social opportunities (48, 49). Initial therapy should be aimed at maximizing the sleep pattern, for example treating nocturnal spasms, nocturia or depression if present. Occupational therapists can be of help in looking at the patient’s routine and reducing fatigue or introducing regular rest periods (fatigue management program). Drug therapy for fatigue is limited. Amantadine in a recent study was shown to be more effective than placebo on one fatigue scale, although it did not show any overall benefit (50). If used, amantadine should be started at 100 mg daily for 1 week, then increasing to 100 mg b.i.d., taking the second dose no later than 4 pm. The main side effects include nausea, anorexia, dizziness, hallucinations and insomnia.

Pemoline, a central nervous system stimulant, has also been tried with limited effect. Adverse effects are frequent and may be sufficient to terminate treatment. The most commonly experienced side effects are irritability, insomnia, anorexia and nausea (51).

Recent studies have also reported the use of the potassium channel blockers, 4-aminopyridine and 3,4-diaminopyridine, for fatigue and heat intolerance. They are thought to work by increasing the action potential amplitude and duration in demyelinated neurons, hence restoring conduction. Improvements in ambulation, visual function and fatigue were noted (52, 53). Although both agents may be useful, side effects do occur, particularly with 4-aminopyridine which crosses the blood-brain barrier. The most serious are seizures but abdominal pain, paresthesia and dizziness may also occur.

Thermal sensitivity

Many MS patients find that their symptoms, particularly fatigue, are much worse in warmer weather. It is thought that raising body temperature causes a slowing of conduction through demyelinated nerve fibers and consequently affects function, often seen as a reduction in visual acuity or loss of power (54, 55). Therapy for these problems is limited but should always include obvious advice such as avoidance of direct sun, frequent cold drinks, air conditioning and cool showers. There
are cooling suits on the market which may help severely affected individuals but these are very cumbersome and expensive (56). During studies of 4-aminopyridine for fatigue it was noted that patients with temperature-sensitive symptoms seemed to do better (57). There is now a slow-release formulation of 4-aminopyridine available for use in future trials which is anticipated to have a similar therapeutic effect but with a wider safety margin (58).

Pain

Pain is estimated to occur in 65% of patients with MS (59-62). Most have chronic pain but an estimated 10% have acute paroxysmal pain, the most common of which is trigeminal neuralgia which occurs 300 times more often in MS patients than in the general population. It usually responds well to carbamazepine, and occasionally misoprostol (prostaglandin E1) may be of benefit (63). Another type of paroxysmal pain is dysesthetic burning pain precipitated by touch, movement or hyperventilation, which may be associated with painful tonic seizures. These may be relieved by baclofen (64).

Commonly, chronic pain may be dysesthetic in nature and involve the extremities. This can be very debilitating for the patient, interfering with mobility, sleep and contributing to depression. The most effective drugs are carbamazepine and the tricyclic antidepressants, particularly amitriptyline, which are best started at low doses in the evening and gradually increased.

Chronic back pain is also common in MS. Apart from the effect of spasticity on the paravertebral musculature the lumbar area also has to cope with abnormal posturing and often an extremely effortful and abnormal gait. This puts great stress on the spine causing degenerative disease. Ideally the physiotherapist should be involved early to help treat spasm if present and to aid correction of posture and gait limiting further damage. Pain relief should include local measures such as heating pads and transcutaneous electrical nerve stimulation. Drug therapy includes short-term nonsteroidal inflammatory drugs and simple analgesia.

Paroxysmal symptoms

Paroxysmal symptoms are infrequent but characteristic of MS. They are of short duration, usually less than 2 min, but can occur many times a day and tend to last for the duration of an average relapse. Symptoms are varied but can include seizures, dysarthria, ataxia or sensory disturbances. Treatment is often effective using a low dose of carbamazepine. Bromocriptine may also be useful (65). Seizures may not require treatment if associated with acute resolving relapses but otherwise are treated with standard anticonvulsants (66).

Current and Future Therapies

In recent years considerable progress has been made in the understanding of the complex immunopathological mechanisms underlying multiple sclerosis. Many of these discoveries have led to the development of new therapeutic strategies. Interferon β-1a and glatiramer acetate (Copaxone®) are now in use in the U.S. and many others are undergoing pivotal trials (67, 68) (Table I).

Interferons

Following the first studies with human interferon by Jacobs in the early 1980s interest has soared in this area (69). Both interferon β-1a and interferon β-1b are now licensed worldwide for relapsing-remitting multiple sclerosis.

Interferon β-1b (IFNB-1b, Betaseron® in North America, Betaferon® in Europe) in a large pivotal study compared two doses (1.6 and 8 million IU) with placebo and demonstrated a reduction of 34% in the relapse rate in patients with relapsing-remitting MS (70, 71), with an even greater effect on moderate to severe relapses. This study also reported stabilization of lesion load seen on T2 weighted magnetic resonance imaging (MRI) and a striking reduction of new lesions as compared to the placebo controls. However, there was no significant difference between the treated and placebo groups when considering progression of disability. 38% of the treated patients went on to develop neutralizing antibodies to IFNB-1b, the detection of which may correlate with loss of effectiveness but may disappear over time (72). On starting IFNB-1b, over 50% of patients will experience systemic side effects of flu-like symptoms including fever, chills and muscle aches. These begin around 4 h after injection and last up to 8 h. They usually abate over the first couple of months of therapy but occasionally are persistent. Other adverse reactions include injection site irritation (rarely necrosis), hepatic impairment and depression. IFNB-1b is given as a subcutaneous injection every other day. The dose is 8 million IU (Betaferon® 0.25 mg).
Table I: Drugs in use or undergoing trials in multiple sclerosis.

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<tr>
<th>Licensed treatment for relapsing-remitting MS</th>
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<tr>
<td>Interferon β-1b</td>
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<td>Interferon β-1a</td>
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<td>Glatiramer acetate (Copaxone®)</td>
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Drugs undergoing pivotal trials

| Interferon β-1b (SP MS + clinically isolated syndromes) |
| Interferon β-1a (SP and PP MS + clinically isolated syndromes) |
| Intravenous immunoglobulin |

Other drugs investigated

| Mitoxantrone (effective in RR MS and 'active' MS) |
| Cladribine (effective in small study of progressive patients) |
| Methotrexate (effective in small study of progressive patients) |
| Sulfasalazine (of no proven benefit) |
| Linomide (adverse effect: ischemic heart disease) |
| Hyperbaric oxygen (of no proven benefit) |
| Deoxyxpergulaline (of no proven benefit) |
| Total lymphoid irradiation (of no proven benefit) |
| Ginkgolide B (of no proven benefit) |
| Acyclovir (nonsignificant reduction in relapse rate) |
| Anti-CD4 (of no proven benefit) |

Future therapies

| Monoclonal antibodies (CAMPATH - 1H) |
| Adhesion molecule therapies |

The study of interferon β-1a (IFNB-1a, Avonex®) looked specifically at the question of whether it affects progression of disability, as measured on Kurtzke’s EDSS (73, 74). The Kaplan-Meier curves suggested lower rates of progression in the treated group compared to the placebo group (p = 0.02). Relapse rate was also reduced in the treated group by 32%. There was a reduction of new enhancing lesions on MRI in the treated group but no significant effect on the total T2 lesion load. Neutralizing antibodies were reported in 22% of the treated patients at 24 months. IFNB-1a was well tolerated by patients, although flu-like symptoms did occur. Injection site reactions were no more frequent in the treated group than the placebo group and there was no increase in the incidence of depression. The drug is given as a once-weekly intramuscular injection at a dose of 6 million IU (Avonex® 30 µg). Recently a study of another IFNB-1a (Rebif®) involving 560 patients with relapsing-remitting MS has been presented (75). It showed a significant reduction in relapse rate, MRI activity and change on the EDSS.

Further studies with the interferons are ongoing and include IFNB-1b (Betaseron®) for secondary progressive MS, IFNB-1a (Rebif®) for secondary progressive MS and IFNB-1a (Avonex®) for relapsing-remitting secondary progressive and primary progressive MS (76). Both Rebif® and Avonex® are also being studied in patients with clinically isolated syndromes (monosymptomatic) to detect if the time to conversion to MS can be delayed.

Glatiramer acetate

Glatiramer acetate (Copaxone®) is a mixture of several polypeptides (L-alanine, L-glutamic acid, L-lysine and L-tyrosine) in a specific ratio. Its therapeutic effect is thought to involve inhibition of the immune response to myelin basic protein. In 1991 a pivotal trial was begun in patients with relapsing-remitting MS (77, 78). The results showed a reduction in relapse rate of 29% in the drug-treated group. There was no difference in progression to sustained disability in either the drug- or placebo-treated group and a very limited MRI study did not show any treatment effect on total T2 lesion load or in the number of new enhancing lesions (79). All patients treated with glatiramer acetate developed antibodies suggesting there was no neutralizing effect (80). It is given as a once-daily subcutaneous injection. Side effects were rare, the most common being injection site reactions consisting of mild erythema or induration (no cases of necrosis reported), and a rare transient systemic reaction consisting of flushing, chest tightness, shortness of breath and anxiety. This tends to last between 30 sec and 30 min and resolves spontaneously.

Intravenous immunoglobulin

The mechanism of action of intravenous immunoglobulin (IVIG) in MS is unknown but is thought to be a combination of T-cell receptor blockade, modulation of cytokine activity and induction of antigen-specific suppressor cells. Animal studies have suggested it might promote remyelination (81). Previous small studies have suggested some effect of IVIG in reducing the relapse rate in relapsing-remitting MS (82-84), and consequently more rigorous trials were commenced.

Fazekas et al. have recently published the results of a double-blind, placebo-controlled study of monthly IVIG infusions in 150 patients for 2 years. Intention-to-treat analysis showed that IVIG treatment had a beneficial effect on the course of clinical disability. EDSS scores (unconfirmed) decreased in the treated group and increased in the placebo group (p = 0.008) (85). IVIG was well tolerated with few side effects, most of which are minor and self-limiting.
Studies were set up at the Mayo Clinic in Rochester, Minnesota to determine whether IVIG may enhance recovery of apparently irreversible neurological deficits such as visual loss from optic neuritis and unrecovered paresis. No effect on unrecovered paresis was found (86).

**Mitoxantrone**

Mitoxantrone is an antineoplastic agent which intercalates with DNA and exerts a potent immunomodulating effect that suppresses humoral immunity and reduces T-cell numbers.

Several small studies have suggested a possible beneficial effect in MS (87-89). Edan et al. recently studied 42 patients with very active MS and randomized them to either mitoxantrone and methylprednisolone or methylprednisolone alone (90). The primary endpoint, i.e., the number of new enhancing lesions on MRI, was significantly in favor of the mitoxantrone group.

Millefiorini et al. reported on 51 patients with relapsing-remitting MS who received monthly infusions of mitoxantrone or saline. The proportion of patients who confirmed progression on EDSS was significantly less in the treatment group (p = 0.02) compared to placebo (91). Several adverse effects were seen in the mitoxantrone-treated group, including alopecia, amenorrhea and nausea. The most worrisome adverse effect is cardiotoxicity which is seen in oncology patients who receive a higher dose than that given in this study. However, the long-term effects of low-dose therapy are not known. Further studies are needed to examine the long-term benefits from mitoxantrone therapy in MS and the risk of cardiotoxicity with these dose regimens.

**Cladribine**

Cladribine is a purine analog which causes apoptosis of lymphocytes. In a 2-year double-blind, placebo-controlled, matched, crossover study, 51 patients with progressive MS received cladribine (92). Average neurological scores and MRI lesion load were stable in the cladribine group but progressed in the placebo group. A larger study of 150 progressive MS patients has recently been completed in the U.S. and Canada (93). Patients received one of two doses of cladribine (0.7-2.1 mg/kg) or placebo subcutaneously. Relapse rate and progression as measured by EDSS were the same in all three groups. On MRI new enhancing lesions were suppressed by 99.3% in the high-dose group, 90.6% in the low-dose group and 69.2% in the placebo group. The authors suggest that the fact that the control group did so well underpowered the study to show an effect on disability. Substantial side effects and toxicity occur with cladribine and should be taken into consideration when evaluating possible benefits in MS.

**Methotrexate**

Methotrexate was tried in multiple sclerosis following its success in the treatment of rheumatoid arthritis which has some immunological similarities to MS. In a recent randomized, double-blind, placebo-controlled, 2-year study of patients with chronic progressive MS, 60 patients were treated with a weekly dose of 7.5 mg methotrexate (94). After 2 years of treatment, 52% of patients on methotrexate showed disease progression compared to 83% of those on placebo. However, disease progression was assessed using a composite score which included change in EDSS, ambulation index and upper limb function (9-hole-peg-test) which is difficult to interpret. No serious adverse effects were experienced and the drug was well tolerated.

**Sulfasalazine**

Sulfasalazine is composed of mesalamine linked covalently to sulfapyridine, and is cleaved to these component parts by bacteria in the colon. Sulfapyridine has been shown to be of benefit in rheumatoid arthritis and is thought to work by suppression of natural killer cells and impairment of lymphocyte transformation.

The 9-center Mayo Clinic-Canadian Cooperative Sulfasalazine Study considered whether sulfasalazine slows disease progression in MS, with sustained disability progression being the primary outcome measure. Results of the study were reported recently as negative (95).

**Linomide**

Linomide is an orally administered quinolone with immunomodulating properties; it stimulates natural killer cell activity and activates several lymphocytic subpopulations. In phase II trials in patients with relapsing-remitting MS (96) and secondary progressive MS (97) it was shown to suppress disease activity as assessed by monthly MRI. Three recent multicenter phase III trials involving different doses of linomide in patients...
with relapsing-remitting and secondary progressive MS were begun but have been abandoned due to an increased incidence in the treatment group of ischemic heart disease.

Miscellaneous
Many drugs have been tried over recent years but have failed to show a beneficial effect in MS or have been complicated by adverse events. Hyperbaric oxygen was recommended for several years and is still in use in many areas. In a review of all the published trials with hyperbaric oxygen, only 8 of the 14 were felt by the authors to be of sufficient quality (98). Only 1 study found any benefit with hyperbaric oxygen (99) and the authors concluded that it could not be recommended in MS.

Several case reports have described dramatic responses to plasmapheresis in patients with acute disseminated encephalomyelitis, steroid unresponsive demyelinating disease or in neurological events associated with connective tissue disorders (100-102). However, in a recent study of 11 patients with secondary progressive MS there was no effect on the primary outcome measure of reduction in the number of gadolinium enhancing lesions (103).

Deoxyspergualine is thought to suppress the maturation of both T- and B-lymphocytes and hence demonstrates immunosuppressive activity. In a large placebo-controlled, crossover study there was no effect on disability progression or in the number of new enhancing lesions seen on MRI between the treated and placebo groups (104, 105).

Early reports suggested that total lymphoid irradiation (TLI) would be a useful form of global immunosuppression, although this has not been confirmed (106). In a study comparing TLI with and without splenic irradiation and combined with steroids, less progression was seen in the TLI + steroids group than the others but no difference was seen between TLI or sham TLI. Side effects were common and included infections and amenorrhea. Almost all patients became cushingoid and there were several fractures, and 1 patient died from unknown causes (107).

Following a pilot study (108) aimed at treating acute relapses of MS with ginkgolide B, a potent inhibitor of platelet activating factor, a large randomized, double-blind, placebo-controlled study was carried out in 104 patients with acute exacerbation of MS. No clinical benefit was seen (109).

Acylovir is effective against the herpes viruses. Since these have been implicated in the possible pathogenesis of multiple sclerosis, a 2-year double-blind, placebo-controlled study of 60 patients was initiated (110). Results were based on an intent-to-treat basis and the primary outcome measure was the exacerbation rate; 34% fewer exacerbations were seen in the treated group but this did not reach significance. The authors suggest that acyclovir treatment may inhibit the triggering of relapses but further investigation is required.

Future approaches
Selective immunosuppression can be achieved using monoclonal antibodies. A multicenter, randomized, double-blind, placebo-controlled study of the chimeric anti-CD4 antibody was carried out in 72 patients with either relapsing-remitting or secondary progressive MS (111). Although all treated patients showed a marked and prolonged reduction in their CD4+ cell count, there was no evidence for arresting disease progression as assessed by the number of new lesions seen by MRI.

No clinical data is yet available on the pan-lymphocyte monoclonal antibody CAMPATH-1H (112). A study involving tumor necrosis factor (TNF)-α receptor and anti-CD4 antibody is underway in Cambridge, U.K.

Oral tolerance is a well-known method of inducing immune tolerance. If a protein is ingested and then the subject is immunized with the same protein a state of systemic hyporesponsiveness exists (113). Following a small pilot study of ingested myelin (114), a large multicenter, randomized, double-blind, placebo-controlled study of 500 patients with relapsing-remitting MS was initiated in the U.S. and Canada, and results have recently been reported to be negative.

As our understanding of the immune processes in MS increases more specific therapies will be suggested. However, influencing one aspect of the immune system may have unanticipated effects on another and actually increase disease activity rather than suppress it. This was seen in a recent open-label study of anti-TNF antibody which produced an immediate increase in MRI activity (115). Other strategies may include inhibition of other inflammatory cytokines such as interleukin-12, or the promotion of downregulating cytokines such as transforming growth factor-β and interleukin-10 (116).

The adhesion molecules are also a potential target for immunotherapy. Their expression at the blood-brain barrier are essential for lymphocytic migration. A phase II trial of a monoclonal antibody
to the $\alpha_4\beta_1$ integrin on T-lymphocytes is underway (117). This inhibits binding of the T-lymphocytes to the counterreceptor on VCAM-1, an adhesion molecule on endothelial cells.

**Comprehensive Management**

A multidisciplinary approach is required to deal with the wide range of disabling and interacting symptoms seen in MS. Following a multidisciplinary team assessment areas of potential functional improvement may be identified and a patient-centered, goal-orientated rehabilitation program planned either in an outpatient or inpatient setting (5).

Freeman et al. recently completed a study assessing the effectiveness of short periods of intensive inpatient rehabilitation and showed that levels of disability and handicap were reduced, at least in the short term (118). A longitudinal study has also been reported looking at the duration of carryover following these admissions. This suggests that even in this group of progressive MS patients, benefits in disability, handicap and quality of life may persist for at least 6 months (119).

Ideally the patient with MS and their carers should be managed in a comprehensive, flexible, community-based service with close links to a neuroscience center. This is usually achieved by ensuring a link worker, or a community care coordinator is established to deal with both the purchaser and provider. Their roles should ideally also include continued education and training for both the patients and more general health professionals (120).

**Conclusions**

Over the last few years there has been marked developments in all areas of management of patients with MS. It is important that these should continue and concentrate both in the areas of symptomatic control and rehabilitation as well as looking at the new and exciting potential treatments. Unfortunately, there are no quick and easy ways of assessing a new drug, as all need to undergo vigorous and often time-consuming clinical trials. It is hoped that, with the advances of MRI, outcome measures can be chosen which reflect underlying disease activity but are very sensitive to change in the disease process and thus shorten trials.

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