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Multiple sclerosis —the treatment options

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The second part of this month's special feature discusses the pharmacological approaches to the treatment of multiple sclerosis and its symptoms

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system (CNS), characterised by inflammation and demyelination of white matter in the brain and spinal cord.¹ Multiple areas of scar tissue (sclerosis) form along the nerve fibres, slowing or blocking the transmission of signals to and from the brain and spinal cord, so that various functions, including movement and sensation, may be lost.² The disease, therefore, is manifested in physical symptoms (relapses and progressive disability), CNS inflammation and cognitive dysfunction. There is great inter- and intra-patient variability of symptoms. MS-related symptoms are shown in Panel 1 (p18).³

MS usually follows a relapsing-remitting course in the early stages of the disease, ie, an acute exacerbation of the disease followed by complete, or near complete, remission. This is known as relapsing-remitting MS (RR-MS). Over time, the disease may enter an irreversible progressive phase, where recovery after a relapse is reduced, and

patients have more disabling symptoms. This is known as secondary progressive MS (SP-MS). There are two other main types of MS — primary progressive (PP-MS), where the disease progresses without relapses, and benign MS, where full recovery occurs after a relapse. A rare category is progressive relapsing disease (PR-MS), which has a similar prognosis to PP-MS.

The three pharmacological approaches to the treatment of MS are management of acute exacerbations, prevention of disease progression, and treatment of chronic symptoms.

ACUTE EXACERBATIONS

An acute deterioration in the neurological state of the patient can arise from an episode of inflammatory demyelination, but can also be caused by other conditions, including concurrent infection (especially urinary tract infection), electrolyte imbalance, fever or drug intoxication.⁴

Most relapses show a degree of spontaneous recovery, but treatment is advised for those relapses that have a severe impact on function. Steroids are the treatment of choice for relapses, usually methyl-

prednisolone 1g daily by intravenous infusion for three days. Alternatively, 500mg daily for five days is sometimes given.

Anecdotally, patients report improvement with low dose oral prednisolone for less severe relapses. However, based on the experience of the optic neuritis treatment trial, only high doses of oral steroids, similar to IV doses, reduce the duration of relapses.⁵ Subsequent studies, also performed in optic neuritis, have shown that equivalent oral doses of steroids can be equally effective.⁶

Before starting steroids, infection should be excluded as a reason for the deterioration in neurological state. This is because steroids have an immunosuppressant action and can exacerbate the infection, which, in some cases, can lead to septicaemia. Steroids reduce oedema and inflammation, resolving the conduction block and therefore reducing the severity of the exacerbation. They do not, however, affect the rate of recovery from a relapse.²

PREVENTING PROGRESSION

Disease modifying treatments are aimed at reducing the frequency and severity of relapses, and slowing the progression of the

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Panel 1: MS-related symptoms³

- Spasticity
- Weakness
- Sensory problems
- Ataxia
- Bladder problems
- Fatigue
- Cramps
- Diplopia
- Visual disturbances
- Bowel problems
- Dysarthria
- Vertigo
- Facial pain
- Poor memory
- Headache
- Neuropsychiatric problems
- Deafness
- Facial weakness
- Dysphagia
- Skin sores
- Blackouts
- Ageusia

disease. There are two types of immunomodulatory agents used as first line treatments, and these are interferon beta and glatiramer acetate.

In January 2002, the National Institute for Clinical Excellence (NICE) published its guidance on the treatment of multiple sclerosis with interferon beta (Avonex, Rebif and Betaferon) and glatiramer acetate (Copaxone).⁷ A detailed appraisal of the clinical and cost-effectiveness of these treatments was undertaken and NICE considered that they did not represent a cost-effective use of NHS resources under the then existing arrangements for purchasing the drugs. In the guidance, NICE also stated that all current NHS patients should continue their therapy until they, and their consultant, considered it appropriate to stop, having regard to the stopping criteria in the Guidelines of the Association of British Neurologists (see Panel 2).⁸ The NICE guidance also applied to all participating patients at the conclusion of a clinical trial (irrespective of whether they were receiving active agent or placebo), and to women whose therapy had been interrupted by pregnancy.

During the preparation of the guidelines, NICE invited the Department of Health (DoH) and the National Assembly for Wales (NAW) to consider what actions could be taken to enable interferon beta and glatiramer to be secured for patients on the NHS in a cost effective manner. The DoH, the NAW, the Scottish Executive and the Northern Ireland DoH, Social Services and Public Safety, reached an agreement with the manufacturers on a risk-sharing scheme for the NHS supply of disease modifying treatments for MS. The scheme involves detailed monitoring of a cohort of patients to confirm the

Panel 2: Summary of the Association of British Neurologists Guidelines for treating MS with interferon beta and glatiramer

Interferon beta

RR-MS

Interferon beta treatment should be offered to patients with RR-MS who fulfil the following criteria:

- Able to walk independently (at least 100 metres without assistance)
- At least two clinically significant relapses in the past two years
- Age 18 years or over

SP-MS

Patients with a non-relapsing SP-MS should not be treated with interferon beta as it is not deemed to be effective. It should only be used in those patients in whom relapses are the dominant cause of the increasing disability. The following criteria should be followed:

- Able to walk at least 10 metres without assistance
- At least two disabling relapses in the past two years
- Any increase in disability, due to slow progression over the past two years, has been minimal
- Age 18 years or over

There is currently no evidence for clinical benefits in PP-MS

Stopping criteria

Discontinuation of treatment may be necessary because of intolerable side effects, or when a pregnancy is planned. Treatment should be discontinued when no longer effective. The following features are likely to indicate lack of efficacy, and should be used as stopping criteria:

- Two disabling relapses within a 12-month period
- Secondary progression with an increase in disability observable over six months
- Loss of ability to walk, with or without assistance, that is persistent for at least six months

Glatiramer

RR-MS

Glatiramer is appropriate treatment to reduce relapse frequency in patients with RR-MS, provided they fulfil the following criteria:

- Able to walk at least 100 metres without assistance
- At least two clinically significant relapses in the past two years
- Age 18 years or over

Glatiramer should not be used to treat SP-MS or PP-MS

Stopping criteria

Discontinuation of treatment may be necessary because of intolerable side effects, or when a pregnancy is planned. Treatment should be discontinued when no longer effective. The following features are likely to indicate lack of efficacy and should be used as stopping criteria:

- Two disabling relapses within a 12-month period
- Development of SP-MS
- Loss of ability to walk, with or without assistance, persistent for at least six months

The stopping criteria should be made known to, and agreed with, the patient before treatment with interferon beta or glatiramer is started. For all patients, it is recommended that a formal review of the treatment takes place at two years to ensure it is still effective

cost-effectiveness of interferon beta and glatiramer acetate. The details of this scheme, and how patients can participate, are set out in Health Service Circular 2002/04.⁹ Panel 3 shows details of the scheme.

■ INTERFERON BETA

Interferon beta is a naturally occurring cytokine produced by various cells, including fibroblasts and macrophages. It is known to have immunomodulatory properties, although its precise mechanism of action in MS remains unclear. It reduces relapse rates in MS patients by approximately a third, but

the effect on disease progression has not yet been established.

There are three preparations licensed for the treatment of MS — Avonex and Rebif (interferon beta-1a) and Betaferon (interferon beta-1b). Table 1 (p20) shows the dosing schedules, licensed indications and main contraindications for these drugs. At the beginning of treatment, adverse effects are common but, in general, they subside with further treatment. The most common adverse effects are an influenza-like syndrome (fever, chills, headache, myalgia, arthralgia, malaise and sweating) and injection site reactions. Neutralising antibodies can develop in patients receiving interferon beta, which can reduce the activity of the drug. Patients require full blood counts, urea and electrolyte monitoring, liver function tests and neutralising antibody assays, before starting, and every three months during treatment.

GLATIRAMER ACETATE

Glatiramer acetate is a synthetic copolymer (formerly known as copolymer-1) with similarities to myelin basic protein. It is administered by daily subcutaneous injection. The main action of glatiramer acetate is thought to be suppression of the immune response against myelin to promote immune tolerance. Glatiramer acetate is licensed for the reduction in frequency of relapses in ambulatory patients with RR-MS, characterised by at least one clinical relapse in the past two years. However, the Association of British Neurologists recommend using it only after two relapses in the past two years.

The recommended dose is 20mg daily. Side effects are mostly mild, the most common being injection site reaction. There may be a transient systemic reaction characterised by facial flushing, chest tightness, palpitations and dyspnoea. Glatiramer is contraindicated in pregnancy and in patients known to be hypersensitive to glatiramer acetate or mannitol.

STOPPING CRITERIA

Discontinuation of treatment for MS patients may be necessary because of intolerable side effects, or when a pregnancy is planned. Treatment should be discontinued when no longer effective. The following features are likely to indicate lack of efficacy, and should be used as stopping criteria:

- Two disabling relapses within a 12-month period
- Development of SP-MS
- Loss of ability to walk (with or without assistance), which persists for at least six months

The stopping criteria should be made known to, and agreed with, the patient

Panel 3: Key elements of the risk-sharing scheme for the supply of disease-modifying treatments for MS (HSC 2002/04)⁹

- The scheme applies to all RR-MS patients and those with SP-MS in whom relapses are the dominant feature. All patients meeting the Association of British Neurologists (ABN) criteria⁸ are eligible to be entered into the scheme, and to receive treatment
- Treatment is only to be initiated by specialist MS centres
- Target outcomes have been set for each product included in the scheme. There would be an acceptable level of cost-effectiveness for the NHS if the targets are met in full
- Outcomes for the cohort of patients will be monitored annually. The cost to the NHS will be adjusted on a sliding scale if outcomes differ from the agreed target for a product
- Monitoring and potential price adjustments under the scheme are expected to continue over 10 years
- There is no bar to neurologists prescribing, and health authorities and NHS trusts funding, interferon beta and glatiramer for patients who do not fall within the ABN guidelines, but in whom treatment is judged to be clinically necessary
- NHS bodies are expected to fund any treatment within the scheme. The choice of treatment should be made on clinical grounds by the prescribing neurologists in consultation with the patient
- Those patients receiving treatment before the scheme was in place, who are not eligible for treatment under the scheme, should continue with treatment until it is appropriate to stop
- The NHS should meet the cost of disease-modifying agents previously being purchased privately from 4 February 2002 by patients whose care is otherwise being provided by the NHS (and the drug was not available to the patients on the NHS because of local funding or prescribing policies)
- Under the scheme, the cost per patient per year will be:

Avonex	£8,502
Betaferon	£7,259
Copaxone	£5,823
Rebif	£7,513 at 22 micrograms three times a week
	£8,942 at 44 micrograms three times a week

before treatment is started. For all patients, it is recommended that a formal review of the treatment takes place at two years from starting therapy to ensure that it is still effective.

OTHER TREATMENTS

Azathioprine, cladribine, cyclophosphamide, ciclosporin, methotrexate and sulfasalazine have all been used to treat MS with varying degrees of success.^{2,10-12} Intravenous immunoglobulins (IVIGs) have also been used. However, the Association of British Neurologists has produced guidelines for the use of IVIGs in neurological diseases, and recommends that they should not be used in MS outside well designed trials.¹³

Mitoxantrone is licensed in the United States for the treatment of RR-MS and SP-MS at a dose of 12mg/m², given by intravenous infusion every three months. Patients who have received eight to 12 doses of mitoxantrone, or a cumulative dose of 140mg/m², generally should not receive additional doses of the drug because of cardiac toxicity. Blood counts and liver function tests should be checked before each dose. The left ventricular ejection fraction should

be checked at the start of treatment, and before each dose once a cumulative dose of 100mg/m² has been reached.¹⁴ Mitoxantrone has been shown significantly to reduce the annual relapse rate by approximately 60 per cent, to delay the time to first exacerbation, and to slow disease progression.³

CHRONIC SYMPTOMS

Multiple sclerosis is associated with a number of chronic symptoms, and these are as follows:

Spasticity Spasticity is a chronic symptom of MS, and it plays a major part in the loss of mobility. With disease progression, spasticity and spasms increasingly affect the muscles of flexion, causing pain and making nursing difficult. Bed sores can result from, and worsen, these spasms.¹⁵ The following treatments are used in varying degrees to treat spasticity.

Baclofen Baclofen is the drug of choice for spasticity. It is a derivative of gamma-aminobutyric acid and acts as an anti-spasmodic agent at a spinal level. It is effective, but its use may be limited by sedation or increasing weakness. A starting dose

Table 1: Licensed indications, doses and contraindications for interferon beta-1a and interferon beta-1b

	Interferon beta-1a		Interferon beta-1b
	Avonex	Rebif	Betaferon
Dosage	30 micrograms (6 million IU) once a week by intramuscular injection	44 micrograms (12 million IU) three times a week by subcutaneous injection. 22 micrograms (6 million IU) is recommended for those patients who cannot tolerate the higher dose	250 micrograms (8 million IU) on alternate days by subcutaneous injection
Licensed indication	Treatment of ambulatory patients with RR-MS characterised by at least two relapses over the preceding three-year period	Treatment of ambulatory patients with RR-MS characterised by at least two relapses over the preceding two-year period	Treatment of ambulatory patients with RR-MS characterised by at least two relapses over the preceding two-year period, and for patients with SP-MS with active disease, evidenced by relapses
Criteria for stopping treatment, according to the summary of product characteristics	Development of SP-MS	Development of SP-MS	Failure to respond
Contraindications	Severe depression (or suicidal thoughts), poorly controlled epilepsy, decompensated liver impairment, hypersensitivity to interferons or human serum albumin, and pregnancy (interferons have been shown to have abortifacient effects in monkeys)		

of 5mg three times a day is recommended, gradually increasing to a therapeutic level, or until intolerable side effects occur. Maximising the bedtime dose may be beneficial as this is usually the time of greatest spasticity. Low starting doses should be used in elderly patients, who may be more susceptible to the side effects on initiation of treatment. A daily dose of more than 100mg (given in three to four divided doses) is not recommended, unless under close supervision. Baclofen should not be stopped abruptly because of the risk of seizures, hallucinations, psychosis, anxiety, confusion and tachycardia. A rebound worsening of spasticity may also occur.

In severe chronic spasticity that is poorly responsive to oral therapy, baclofen can be administered intrathecally via a pump. The pump is implanted in the chest or abdominal wall tissue and a catheter connects the pump to the intrathecal space. Patients undergo an

initial screening phase to determine their response to test bolus doses, followed by a dose titration phase. The initial total daily infused dose is determined by doubling the bolus dose which gave a significant response, and administering it over 24 hours. After the initial 24 hour period, the dose may be adjusted to achieve the desired clinical effect.

The main adverse effects are pump malfunction, and kinking or dislodgement of the catheter. The reservoir in the pump must be refilled aseptically by trained and qualified personnel because care is needed to avoid discharging the contents of the catheter into the intrathecal space.

Tizanidine Tizanidine is a newly introduced α_2 -adrenoceptor agonist. It acts within the central nervous system at supra-spinal and spinal levels. Tizanidine is used as an alternative to baclofen, especially if baclofen

use is limited by adverse effects because it tends to produce less muscle weakness. Treatment starts at a daily dose of 2mg. This is increased (in increments of 2mg) according to response at intervals of three to four days. Tizanidine has a relatively short duration of action and, therefore, the daily dose is usually given in three or four divided doses. A total daily dose of 36mg should not be exceeded, although it is not usually necessary to exceed 24mg daily.

Benzodiazepines Diazepam and clonazepam can be used to treat spasticity. Their usefulness is limited by sedation and dependency. However, benzodiazepines may be of most use at night, where sedation can be of help.

Dantrolene Dantrolene has a direct action on skeletal muscle and is effective in reducing spasticity. However, it can cause muscle weakness and is often poorly tolerated. An initial dose of 25mg is recommended, increasing at weekly intervals to a maximum of 100mg four times a day. Therapeutic effect can take a few weeks to develop. However, because of the drug's hepatotoxic effects in long-term use, treatment should be discontinued if there is no benefit after four to six weeks.

Lack of co-ordination and cerebellar tremor Another chronic symptom of MS is lack of co-ordination and cerebellar tremor. This can lead to disability because of loss of limb function, even where strength is maintained. Minor tremor may respond to weights on the affected limb. Many drugs have been tried, with limited success. These include isoniazid (600–1,200mg daily),^{16,17} which is given with pyridoxine to prevent peripheral neuropathy, and ondansetron. However, benefit with ondansetron therapy has only been shown with intravenous use.^{18,19} Beta-blockers and clonazepam have also been used.

Fatigue Fatigue is a common complaint affecting most patients with MS. In general, fatigue does not respond well to pharmacological intervention and, therefore, lifestyle adaptations are usually necessary.

Drugs that have been tried include amantadine (100mg twice a day), pemoline (no longer available in the UK), 4-aminopyridine, 3,4-diaminopyridine, and fluoxetine (10-40mg a day).²⁰⁻²⁴

Pain MS-related pain is usually neuropathic. Treatments that are used include amitriptyline, carbamazepine and gabapentin. Gabapentin (at a low dose of 300-400mg a day) has also been reported to help improve spasticity and gait, but only in two patients.²⁵ Cannabis and its pharmacological derivatives are currently undergoing a number of trials in MS. Cannabis is reported to alleviate spasticity,

pain and tremor.²⁶ A large trial is being undertaken at Derriford Hospital in Plymouth. The Cannabis in MS trial will look at whether cannabis or one of its derivatives can help the muscle stiffness and spasms that affect MS patients. Results are likely to be published in 2003.

Bladder dysfunction Urinary symptoms of frequency, urgency and urge incontinence are common in MS, and occur as a result of detrusor instability and spasm. With disease progression, loss of detrusor tone causes urinary retention, frequency and incontinence. Oxybutynin is an anticholinergic agent that also acts as an antispasmodic on the smooth muscle of the bladder, which helps to inhibit bladder contraction. Tolterodine, a competitive cholinergic receptor antagonist with bladder selectivity, can also be used. Both are contraindicated in urinary retention. Desmopressin can be used for the treatment of nocturnal enuresis.

Bowel dysfunction Constipation is a common problem in MS patients who have limited mobility. An adequate fluid intake and a high fibre diet are necessary. Stimulant laxatives, such as senna, are also commonly used. Diarrhoea can be managed with a bulk forming agent. Loperamide may also be useful.

Sexual dysfunction Erectile dysfunction is common in male patients with MS. This can be treated with sildenafil, which can be prescribed on the National Health Service.²⁷

Mood disorders Depression is more common in MS patients than in the general population.²⁸ It usually responds to standard antidepressant treatment. Several of the treatments used in MS (eg, interferon beta) can themselves cause depression, and could be altered if appropriate.

SUMMARY

Although there are disease modifying agents available, they have not been shown to prevent disease progression. Therefore, symptomatic treatment, along with supportive measures and rehabilitation, are a major part of the treatment of MS.

Credit for Learning begins on p29

REFERENCES

- Green B, Mynes S. Issues in MS. *Pharm J* 1999;262:699-701.
- Clegg A, Bryant J, Milne R. Disease modifying drugs for multiple sclerosis: a rapid systematic review. *Health Technology Assessment* 2000;4:1.
- Hartung HP, Gonsette R. MIMS Study Group. Mitoxantrone in progressive multiple sclerosis. A placebo-controlled, randomised, observer-blind European phase III multicentre study — clinical results (abstract OR 207). *Multiple Sclerosis* 1998;4:325.
- Toosy A, Thompson A. Multiple sclerosis: the disease and its treatment. *Pharm J* 2000;264:694-700.
- Beck RW, Cleary PA, Anderson MMJ, Keltner JL, Shults WT, Kaufman DI 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;326:581-8.
- Sellebjerg F, Nielsen HS, Frederiksen JL, Olesen J. A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis. *Neurology* 1998;51:529-34.
- Technology Appraisal Guidance number 32. Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. London: National Institute for Clinical Excellence; 2002 (January).
- Association of British Neurologists. Guidelines for the use of beta interferon in multiple sclerosis. London: Association of British Neurologists; 1999.
- Health Service Circular 2002/04. Cost effective provision of disease modifying therapies for people with multiple sclerosis. London: Department of Health; 2002.
- Yudkin PL, Ellison GW, Ghezzi A, Goodkin DE, Hughes RA, McPherson K et al. Overview of azathioprine treatment in multiple sclerosis. *Lancet* 1991;338:1051-5.
- Noseworthy JH, Gold R, Hartung H. Treatment of multiple sclerosis: recent trials and future perspectives. *Curr Opin Neurol* 1999;12:279-93.
- Bryant J, Clegg A, Milne R. Systematic review of immunomodulatory drugs for the treatment of people with multiple sclerosis: Is there good quality evidence on effectiveness and cost? *J Neurol Neurosurg Psychiatry* 2001;70:574-9.
- Association of British Neurologists. Guidelines on intravenous immunoglobulins (IVIGs). London: Association of British Neurologists; 2001.
- Mitoxantrone receives multiple sclerosis licence. *Am J Hosp Pharm* 2000;57:2039-40.
- Richards RG, Sampson FC, Beard SM, Tappinham P. A review of the natural history and epidemiology of multiple sclerosis. Implications for resource allocation and health economic models. *Health Technology Assessment* 2002;6:9.
- Morrow J, McDowell H, Ritchie C, Patterson V. Isoniazid and action tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1985;48:282-3.
- Hallett M, Lindsey JW, Adelstein BD, Riley PO. Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. *Neurology* 1985;35:1374-7.
- Rice GP, Lesaux J, Vandervoort P, Macewan L, Ebers GC. Ondansetron, a 5-HT₃ antagonist, improves cerebellar tremor. *J Neurol Neurosurg Psychiatry* 1997;62:282-4.
- Rice GP, Lesaux J, Ebers G. Ondansetron versus placebo for disabling cerebellar tremor: final report of a randomised clinical trial. *Ann Neurol* 1999;46:493.
- Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technology Assessment* 2000;4:
- Krupp LB, Coyle PK, Doscher C, Miller A, Cross AH, Jandorf L et al. Fatigue therapy in multiple sclerosis: results of a double blind, randomised, parallel trial of amantadine, pemoline and placebo. *Neurology* 1995;45:1956-61.
- Weinshenker BG, Penman M, Bass B, Ebers GC, Rice GP. A double blind, randomised, crossover trial of pemoline in fatigue associated with multiple sclerosis. *Neurology* 1992;42:1468-71.
- Polman CH, Bertelsmann FW, van Loenen AC, Koetsier JC. 4-Aminopyridine in the treatment of patients with multiple sclerosis. Long-term efficacy and safety. *Arch Neurol* 1994;51:292-6.
- Sheehan GL, Murray NM, Rothwell JC, Miller DH, Thompson AJ. An open-labelled clinical and electrophysiological study of 3,4-diaminopyridine in the treatment of fatigue in multiple sclerosis. *Brain* 1998;121:967-75.
- Duvenhsky A, Perel AB. Gabapentin for relief of spasticity associated with multiple sclerosis. *Am J Phys Med Rehab* 1998;77:451-4.
- Williamson E, Evans F. Cannabinoids in clinical practice. *Drugs* 2000;60:1303-14.
- Rudick RA, Cohen JA, Weinstock-Guttman B, Kinkel RP, Ransohoff RM. Management of multiple sclerosis. *N Engl J Med* 1997;337:1604-11.
- Whitlock FA, Siskind MM. Depression as a major symptom of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1980;43:861-5.