Late-onset multiple sclerosis part two: treatment and management

As part one outlined in the August issue (Vol 36:8), differential diagnosis of late-onset MS (LOMS) may be difficult and includes cerebro-spinal vascular syndromes, hypertension-related disorders, compressive myelopathies, primary or secondary vasculitis, metabolic diseases, degenerative and nutritional syndromes. In the second and final part of the series, Dr Nabil Aly discusses management and drug therapy treatments for LOMS.

Multiple sclerosis (MS) with clinical onset after 50 years old is unusual and frequently misdiagnosed. Late-onset multiple sclerosis (LOMS), defined as the first presentation of clinical symptoms in patients over 50, is not as rare a phenomenon as previously thought, since in various studies the prevalence ranges between four per cent and 9.6 per cent studies. Clinical presentation and course seem also to be different than in MS occurring between 20 and 50 years old. There is tendency to have high frequency of progressive course, motor function involvement and poor prognosis. The goal of therapy in patients with LOMS is to prevent relapses and progressive worsening of the disease. Spontaneous recovery is rare when neurologic deficits have persisted for longer than six months, and there are no known therapies that promote regeneration and reverse fixed neurologic deficits. Therefore, disease-modifying therapy should be considered before neurologic deficits have persisted longer than six months. Decisions in individual patients should be based both on the course of the patient’s disease and on the probability of severe disabling disease.

The vast majority – more than 50 per cent – of patients have relapsing/remitting MS during the early years and secondary-progressive later. They have the best responses to treatment. Patients with progressive disease are less responsive to treatment. Disease-modifying therapy should be considered early in the course for patients with an unfavourable prognosis. The unfavourable prognostic markers related to more rapid worsening of disease can be used to select patients for treatment. Patients who have multiple cranial magnetic resonance imaging (MRI) lesions at the time of their first symptoms are much more likely to have major disability later on. Therefore, in addition to the clinical features, the findings on cranial MRI are useful in selecting patients for early treatment.

Approximately 10 per cent of patients have relatively benign disease, so not every patient should receive disease-modifying therapy. During the acute attack or relapse of MS, steroids are the mainstay of therapy. Cortico-steroids have immunomodulatory and anti-inflammatory effects that restore the blood/brain barrier, reduce oedema and possibly improve axonal conduction. Steroid therapy shortens the duration of the relapse and accelerates recovery, but whether the overall degree of recovery is improved or the long-term course altered is not known. In addition, other therapy lines such as physiotherapy, vaccination and symptomatic treatment should be considered.

MS, whether late-onset or not, causes a large variety of symptoms and the treatments for these are equally diverse. Most symptoms can be treated.
and complications avoided with good care and attention from medical professionals. Preventing complications such as pneumonia, bed sores, injuries from falls or urinary infection requires attention to the primary problems that may cause them. Spasticity is a common problem and is treated with baclofen, Zanaflex® or dantrium.

**Symptomatic treatment of acute relapse**

Corticosteroids are the mainstay of treatment for acute relapses of MS. Corticotropin was demonstrated to help recovery from relapse, but it has been largely replaced by high-dose intravenous methylprednisolone because the latter has a more rapid onset of action, produces more consistent benefits, and has fewer side effects. For moderate-to-severe relapses, 1000mg of methylprednisolone per day by intravenous infusion for three to five days followed by 60mg of oral prednisolone per day, with tapering of the dose over a period of 12 days, accelerates neurologic recovery.

In the optic neuritis, intravenous methylprednisolone found to reduce by approximately 50 per cent the risk of an attack leading to the diagnosis of MS during the two-year follow-up. This effect was most evident in patients at highest risk for subsequent relapse — those with multicentric brain lesions on MRI. Intravenous methylprednisolone delayed — but did not stop — the development of MS after optic neuritis.

**Disease-modifying therapy**

Interferon beta is the treatment of choice for patients with relapsing/remitting MS. Two forms of recombinant interferon beta: 1a and 1b. Interferon beta-1a is a glycosylated, recombinant mammalian-cell product, with an amino-acid sequence identical to that of natural interferon beta. Interferon beta-1b is a non-glycosylated recombinant bacterial-cell product in which serine is substituted for cysteine at position.

Interferon beta-1b and beta-1a were tested in a multicenter trials involving patients with relapsing/remitting MS and mild-to-moderate disability and as compared to treatment with placebo. Treatment with the higher dose beta-1b and beta-1a reduced the annual relapse rate by 31 per cent and 32 per cent respectively, with fewer gadolinium-enhanced lesions on MRI. There was also a significant reduction in disease activity, defined as the finding of new or enlarging lesions in serial MRIs; and beta-1a significant lowered the probability of progression of disability and of severe disability. Both types of interferon beta are usually well tolerated. The most common side effects are influenza-like symptoms for 24 to 48 hours after each injection, and these usually subside after two to three months of treatment. The variable biologic response to interferon beta suggests that the dose could be individualised. Although interferon beta therapy is effective, a risk/benefit analysis must be done in each patient. The cost of therapy and the uncertain long-term risks may outweigh the benefits in patients with mild MS and a favourable prognosis.

Whether long-term therapy should be started at the time of the first attack and what constitutes the optimal duration of therapy are not known. The best preparation of interferon beta and the long-term benefits of such therapy remain controversial. Both interferon beta-1a and interferon beta-1b reduce the relapse rate and disease activity on MRI, but interferon beta-1a appears to be better tolerated. In addition, interferon beta-1a results in less progression of disability, suggesting that long-term therapy will lessen the eventual impact of the disease. In the UK, as a result of National Institute for Health and Clinical Excellence (NICE) announcement that interferon beta and glatiramer acetate are not cost effective treatments for MS and could not be recommended for NHS funding, the Department of Health and the manufacturers developed a ‘risk sharing scheme’ aimed at providing these drugs more cost effectively. Treatment will be provided to ambulating patients with two or more disabling relapses in the past two years (about 15 per cent of all patients with MS) and their progress monitored over 10 years. However, the scheme has several scientific and practical problems that might limit its ability to improve the care of patients in the long term.

**Glatiramer acetate (GA)**

Glatiramer acetate is a putative auto-antigen in MS, synthesised as an immuno-chemical mimic of myelin basic protein. It represents an alternative to interferon beta therapy for patients with relapsing/remitting MS and may be most useful for patients who become resistant to interferon beta treatment owing to serum interferon beta-neutralising activity. The most common side effect is mild reactions at the injection site, which may occur in up to 90 per cent of patients.
Azathioprine
Azathioprine, a purine analogue, depresses both cell-mediated and humoral immunity. It should be considered in patients with relapsing/remitting MS who do not respond to therapy with interferon beta or glatiramer acetate, particularly in those with recurrent inflammatory myelitis.

Mitoxantrone
Mitoxantrone is a synthetic anthracenedione used for the treatment of worsening relapsing/remitting or progressive MS. It is associated with a variety of potential toxicities including cardiotoxicity. At the recommended dosage, mitoxantrone appears to have a low potential to cause cardiotoxicity. Intravenous mitoxantrone reduces the relapse rate and slows progression of the disease in patients with worsening relapsing/remitting or secondary progressive MS, thus providing a new option for the management of these patients. The drug is generally well tolerated at the recommended dosage, although potential cardiotoxicity limits the total cumulative dose to 140mg/m\textsuperscript{2}. Further studies are warranted to determine which patients with worsening MS are most likely to benefit from mitoxantrone treatment and to more fully define the long-term safety and tolerability of mitoxantrone, including the use of concomitant cardioprotectants to extend the therapeutic lifespan of the drug\textsuperscript{19}.

Intravenous immune globulin
Intravenous immune globulin has been used successfully in neuroimmunologic disorders, including acute and chronic inflammatory demyelinating polyradiculopathy and myasthenia gravis, but its role in MS is not yet clear.

Other immunomodulator agents
Treatment for chronic progressive MS has usually consisted of non-specific immune suppression and has been of only moderate benefit. Low-dose oral methotrexate is relatively non-toxic and effective in inhibiting both cell-mediated and humoral immunity or as a result of its anti-inflammatory effects. It provides an alternative treatment for patients with chronic progressive MS, and should be considered for those with progressive deterioration. Cyclophosphamide, a potent cytotoxic and immunosuppressive agent, may be most appropriate for patients with rapidly progressive disease who do not respond to the less toxic methotrexate. The moderate clinical benefits of cyclosporine, a potent immunosuppressive drug that inhibits several steps in the activation of T-cells, appear to be outweighed by its toxicity (nephrotoxicity and hypertension).

Combination therapy
Despite the efficacy of immunomodulating agents in the treatment of MS, many patients continue to show progression of disability, breakthrough relapses and active disease on MRI. Therefore, clinicians have employed a variety of combinations of agents in an attempt to decrease disease activity in those with active disease, despite standard immunomodulatory therapy. Although a variety of combination therapies have been used in clinical practice, there is a paucity of data available to guide clinical decision-making. The combination of mitoxantrone and interferon beta (IFNbeta) appears safe in short-term studies from a toxicity standpoint and is associated with a reduction in relapse rates, a decrease in the frequency of enhancing lesions, and a decrease in T2 lesion burden.

Other combinations that appear safe in preliminary studies include IFN beta-1a and methotrexate, IFNbeta-1a and azathioprine, and mitoxantrone plus methylprednisolone. The decision to use combination therapy in patients with a suboptimal response to monotherapy should be considered early and not be delayed until disability becomes advanced\textsuperscript{20}.

Other treatment lines
Physiotherapy helps the patient with MS to strengthen and retrain affected muscles; to maintain range of motion to prevent muscle stiffening; to learn to use such assistive devices as walking stick and walking frames; and to learn safer and more energy-efficient ways of moving, sitting, and transferring. In addition, exercise is an important part of maintaining function for the patient with MS. Swimming is often recommended, not only for its low-impact workout, but also because it allows strenuous activity without overheating.

Occupational therapy helps MS patients adapt to their environment and adapt the environment to themselves. The occupational therapist may suggest alternate strategies and assistive devices for such daily activities as dressing, feeding,
washing. They can also evaluate the home and work environment for safety and efficiency improvements that may be made. Vaccination against influenza may be considered as it can prevent respiratory complications, and contrary to earlier concerns, is not associated with worsening of symptoms. Training in bowel and bladder care may be needed to prevent or compensate for incontinence. Intermittent catheterisation, where a catheter is used to periodically empty the bladder, is effective in controlling bladder dysfunction.

Chronic pain may improve once a relief of spasticity is achieved using baclofen and diazepam or botulinum toxin injection. Other more acute types of pain may respond to carbamazepine. Low back pain is common, secondary to increased use of the back muscles to compensate for weakened legs, and may improve on physiotherapy and/or general analgesics.

**Conclusion**

Multiple sclerosis with clinical onset after 50 years old is not as rare a phenomenon as previously thought. A confident and accurate diagnosis of MS is important, but a specific diagnostic test for the disease does not exist. The main goal of therapy is to prevent relapses and progressive worsening of the disease. Steroid therapy is the mainstay of acute relapse treatment and disease-modifying therapy should be considered early in selected patients, before neurological deficits persist.

**Key points**

- MS is a chronic autoimmune disorder affecting movement, sensation and bodily functions.
- Late onset multiple sclerosis (LOMS), in patients over 50, is not a rare phenomenon; its prevalence ranges between 4 per cent and 9.6 per cent.
- Steroid therapy is the mainstay of acute relapse treatment.
- Disease-modifying therapy should be considered early in selected patients, before neurological deficits persist.
neurological deficits persist. Management decisions in individual patients should be based both on the course of the patient’s disease and on the probability of severe disabling disease.

Conflict of interest: none declared.