During recent years, with the advent of disease-modifying drugs (DMDs), the way that multiple sclerosis (MS) is approached by neurologists has started to change. Up until the mid 1990s, it was only possible to treat relapses and manage patients’ symptoms. A growing body of evidence suggests that DMDs can reduce the rate of relapse and slow disease progression. However, symptom control remains essential for MS sufferers. As the complexity of therapies for MS increases, pharmacists must be prepared to assume a more active role in monitoring the effectiveness and side effects of the medicines used, and any potential drug interactions.

Corticosteroids
Managing an acute relapse of MS involves treating the relapse itself and any residual symptoms. Standard treatment for a relapse is methylprednisolone 0.5–1g administered by intravenous infusion (or 0.5–2g given orally) daily for three to five days. Corticosteroids reduce the duration of a relapse but do not influence the extent of recovery (which occurs eventually even without steroids) and have no impact on disease progression.

The mechanism of action of corticosteroids as potent immunosuppressants in the treatment of MS is not fully understood. Hypotheses include that they inhibit the production and activity of pro-inflammatory cytokines, including some interleukins (IL-1, IL-2 and IL-6). Overall, they inhibit endothelial activity and suppress cytokine, leukotriene and prostaglandin production — thereby suppressing the body’s inflammatory response.

The long-term side effects of corticosteroid treatment, such as osteoporosis, diabetes and "Cushingoid effects", mean that most clinicians do not prescribe more than two courses per year per patient (although guidelines from the National Institute for Health and Clinical Excellence state that up to three courses per year is safe).

Disease modifying drugs
In 1993, the Food and Drug Administration approved the use of interferon beta-1b — the first licensed DMD capable of altering the course of MS. It received a European licence in 1995. Since then, several others have been approved for use.

Interferons
The interferons are intracellular messengers that belong to a subgroup of cytokines. Their effects on patients with MS have been studied since the late 1970s. Two types of interferons exist: type I, which includes interferon alpha (IFN-α) and interferon beta (IFN-β); and type II, which includes interferon gamma (IFN-γ).

IFN-γ is an immune enhancer known to aggravate MS by stimulating patients’ immune response and...
precipitating relapses. Several studies have demonstrated that IFN-β blocks the effects of endogenous IFN-γ. Other studies have shown that treatment with IFN-β-1b reduces the rate of relapse in MS patients by about one third and that its ability to limit disability is significant for patients with severe relapsing remitting or secondary progressive MS. Magnetic resonance imaging conducted at the end of a five-year study revealed that patients treated with IFN-β-1b developed 75% fewer new brain lesions compared with placebo.

In theory, the earlier IFN-β-1b is used in the course of a patient's MS, the more beneficial it might be expected to be. However, this strategy risks the risk that some patients, who experience initial symptoms but would not necessarily develop MS, will be treated unnecessarily.

The importance of early recognition and treatment of patients who have symptoms suggestive of MS has been emphasised in three trials (CHAMPS, ETOMS and BENEFIT). In these studies, 45–50% of untreated patients with a confirmed “clinically isolated syndrome” went on to develop MS over a two to three year period. This compared with 28–35% of those treated with IFN-β-1a or IFN-β-1b.

IFN-β does not alter the progression of primary progressive or secondary progressive MS. It can reduce relapse rates in patients with secondary progressive MS if the condition is associated with high relapse rates (although this form of disease is rare). Nonetheless, the medicines are usually non-toxic (the main side effects include hyperthermia, injection site reactions and flu-like symptoms) usually non-toxic (the main side effects include hyperthermia, injection site reactions and flu-like symptoms) and evidence for their benefit has been confirmed so their use by neurologists is becoming more common.

IFN-β-1a IFN-β-1a has been analysed in the PRISMS trial — a multicentre, placebo-controlled study involving 560 patients with relapsing remitting MS. Patients were randomised to receive 22µg IFN-β-1a, 44µg IFN-β-1a or placebo by subcutaneous injection three times a week for two years. Results showed that patients in the treatment groups (22µg and 44µg) experienced a significant reduction in relapse rate (27% and 33%, respectively) compared with placebo.

Resistence In a North American study, 35% of patients with relapsing remitting MS developed neutralising antibodies to interferons within two years of starting treatment. The beneficial effects on reducing relapse rates diminished in such patients.

This issue might be resolved if an immunosuppressant is given concurrently with the interferon. However, its impact on clinical outcomes remains unproven. As such, no national organisation currently recommends measuring antibody levels routinely for patients receiving interferon.

Glatiramer acetate Glatiramer acetate emerged from attempts by one laboratory to generate a compound that induces experimental allergic encephalopathy (EAE; an animal model of MS) by mimicking myelin basic protein. However, rather than stimulating the immune system to attack myelin, the opposite effect occurred. A recent industry-funded trial showed that early treatment with glatiramer for patients presenting with a clinically isolated syndrome and brain lesions (detected by MRI) was successful in delaying progression to clinically definite MS.

Glatiramer is believed to exert its effect by reducing the extent to which lymphocytes react with myelin. Furthermore, protection from relapses gradually increases with time. Disease stability is expected in about 70% of those treated for at least two years and is expected to last for at least seven years.

Mitoxantrone In 2000, mitoxantrone became the first medicine to be approved in the US to treat secondary progressive MS. (In the UK, it is used off-licence.) It is a potent immunosuppressant with antineoplastic activity (it inhibits DNA and RNA synthesis by intercalating into DNA) and has a growing body of evidence confirming its benefit for patients with MS. Mitoxantrone can reduce patients’ annual relapse rates and either improve or stabilise relapsing remitting and secondary progressive MS. Although probably more effective than interferon, its cumulative cardiotoxicity means its use can only be justified when treating aggressive forms of MS.

Azathioprine Potent immunosuppressant azathioprine has been used to treat MS since the 1960s. Based on a meta-analysis of azathioprine versus placebo, it is unlikely

Emerging therapies

The increased understanding of multiple sclerosis (MS) and the use of magnetic resonance imaging (to analyse “lesion load”) are aiding investigations into new therapies. Several oral medicines are in the pipeline. These include:

- **Fingolimod** This novel immunosuppressant was shown in one study to keep 77% of MS patients relapse free for up to two years of treatment.
- **Laquinimod** A phase II trial involving patients with relapsing remitting MS demonstrated a reduction in the number of new lesions for those receiving laquinimod compared with those receiving placebo.
- **Cladribine** A phase III trial involving 1,326 patients (currently unpublished) showed cladribine to reduce relapse rates by 58% when compared with placebo. The researchers also found a 30% reduction in disease progression. A European licence for cladribine was applied for in July 2009 and it is hoped that the licence will be granted by mid 2010.
- **Alemtuzumab** A recent trial showed that patients taking this monoclonal antibody experienced a 74% reduction in relapse rates compared with those taking interferon beta-1a and, more importantly, a 70% reduction in accumulating disability over three years compared with the interferon group.

The therapeutic role of immunoglobulins in MS remains unresolved with optimal dosing yet to be established. Trials suggest a modest effect on relapsing remitting MS comparable to interferon beta but their effects on secondary progressive MS are being investigated.

Bone marrow transplantation has been shown to improve or stabilise severe MS in 63% of cases. Other targets for future treatments include promoting remyelination and inhibiting lymphocyte adhesion to, and migration through, the blood-brain barrier.
that azathioprine is more effective than interferon. Since azathioprine also causes more toxic side effects, it is reserved for treating more aggressive forms of MS. Trials have indicated that a significant effect on relapse rates only occurs once patients (including those with progressive disease) have been treated for four years. It would appear, therefore, that azathioprine might slow the progression of disability after a long period of treatment but has less impact on reducing relapse rates.

Natalizumab

Monoclonal antibody natalizumab binds to protein called α₄β₁ integrin, which is highly expressed on the surface of lymphocytes and prevents the lymphocyte interacting with its cognate receptor on the endothelium of the blood-brain barrier. This prevents the passage of lymphocytes into the CNS where they would otherwise form part of the immune response that leads to inflammation (see accompanying article, p435).

Natalizumab has been shown to reduce relapse rates by 68% after one year when compared with placebo and has generated much excitement among neurologists by demonstrating superior efficacy to interferons. This led to a US licence being granted in 2006 based upon unpublished interim data for relapsing remitting MS. However, the drug was withdrawn from the market several months later when two cases of progressive multifocal leucoencephalopathy were diagnosed in a trial combining it with IFN-β-1a. Subsequently, in 2007, natalizumab was “regranted” a licence to be used as monotherapy for patients with severe relapsing remitting MS.

Symptom control and rehabilitation

In the early 1990s there were no licensed treatments available that could slow the onset of disability or reduce relapse rates for patients with MS. Now IFN-β and monoclonal antibodies are available, but their effects on disease progression are modest. Consequently, managing the symptoms of MS remains an important role for clinicians as the disease progresses.

Fatigue

Fatigue is common among MS patients but must be distinguished from depression. The cause of fatigue must be determined first because “MS fatigue” is treated differently to fatigue caused by other factors (eg, medicines, nocturia or painful night spasms — all of which can impair sleep).

Neurostimulant amantadine has been used off-licence to treat MS fatigue for many years — with variable
results. More recently, a preliminary study has shown modafinil to offer some relief for MS fatigue. Another group of medicines, the aminopyridines, have been used by some neurologists but have yet to demonstrate efficacy for this indication.1

Genitourinary and bowel dysfunction Bladder, bowel and sexual dysfunction are common features of MS. In bladder disturbance, hyper-reflexia leads to urinary incontinence. Ultrasound is used to determine the residual volume of the bladder after voiding. If the volume is less than 100ml, anticholinergic treatment (eg, oxybutynin or tolterodine) can be started to prevent, or at least reduce, urinary incontinence. If the volume exceeds 100ml, the addition of anticholinergics could precipitate urinary retention so catheterisation is necessary. Wherever possible, patients should be taught self-catheterisation methods.1,15

MS patients often experience constipation and this can be worsened if a patient reduces his or her fluid intake to avoid urinary incontinence. This usually responds well to a combination of stimulant, osmotic and bulk-forming laxatives. Anal plugs can be prescribed for faecal incontinence, which is less common.1,15

Nervous system disorders Spasticity can be treated with oral medicines such as baclofen, tizanidine, diazepam and clonazepam, or with local injections of botulinum toxin (performed by specialists). The aims of management are to improve function, relieve pain and ease care but not to remove spasticity completely.1,15

Ataxia (a lack of co-ordination) is a complex, resistant and frustrating symptom of MS, which responds poorly to treatment. Medicines that have been used include ioniazid (with pyridoxine), clonazepam, primidone, propranolol and, more recently, gabapentin and isoniazid (with pyridoxine), clonazepam, primidone, propranolol and, more recently, gabapentin and ondansetron, although there is no published evidence of their benefit. Surgical intervention, such as a thalamotomy or thalamus stimulation, has also been used with variable success in refractory cases.1,15

Most MS patients experience pain, which is acute or paroxysmal in 15% of cases and chronic in the remainder. Medicines that have been tried, with varying degrees of success, include amitryptiline, carbamazepine, gabapentin, pregabalin, phenytoin and lamotrigine. Refractive cases may require referral to a pain clinic.1,15

Acute vertigo can be managed using prochlorperazine or cinnarizine, whereas for chronic cases physiotherapy (particularly Cawthorne-Cooksey exercises) can be more beneficial.1,15

Dysphagia Mild dysphagia can occur in up to 45% of MS patients — these should be referred to a speech and language therapist. For severe cases, percutaneous endoscopic gastrostomy (PEG) might be necessary to allow safe feeding.1,15

Conclusion Newer treatments for MS (DMDs) focus on slowing disease progression and reducing relapse rates. Although these medicines require careful monitoring, they have provided encouragement to patients and professionals alike. Despite the development of these new treatments, symptomatic control, physiotherapy and rehabilitation remain the cornerstone of managing this debilitating condition.

References