Current Therapy of Multiple Sclerosis

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The list of medications for both immune modulation and symptomatic relief continues to grow. Ideally, however, drug therapy should be part of a multidisciplinary approach that also includes such elements as patient education and physical therapy.

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Case 1: Presentation

A 29-year-old woman sought a second opinion from a neurologist regarding treatment of her multiple sclerosis. Dizziness and slurred speech had occurred four years earlier, three months after the delivery of her first child. She was treated for labyrinthitis, and the symptoms resolved within two weeks.

Five months ago, she had noted some weakness in her right leg while exercising. She saw a neurologist, who ordered magnetic resonance imaging (MRI) of the brain; it showed three lesions in the periventricular white matter and one in the cerebellum. Following lumbar puncture, oligoclonal bands were detected in the cerebrospinal fluid (CSF).

The first neurologist diagnosed multiple sclerosis and treated the patient with intravenous methylprednisolone, 1 g/day for three days. Her leg weakness resolved and she had no further symptoms.

She subsequently attended a Multiple Sclerosis Society workshop for newly diagnosed patients, which prompted her to consult another neurologist for further advice on treatment. This examination showed nystagmus on lateral gaze and a positive Babinski sign on the right.

This patient's illness is a classic case of multiple sclerosis (MS). Onset typically occurs in young adult life, and 70% of patients are women. Disease control is better during pregnancy than during the postpartum period—the three to four months after delivery in particular is a time of increased risk of relapse. The reason for this is not fully understood, but it appears to involve an interplay of endocrine changes and immune activity.
The mode of onset in this patient was also typical. First episodes of MS are often marked by brainstem abnormalities, such as double vision or labyrinthitis. Her second episode, which involved a different part of the central nervous system (CNS), illustrates the shifting pattern of MS symptoms. Neurologic examination generally reveals evidence of multiple CNS lesions; in this case, the positive Babinski sign indicates corticospinal tract disease.

MRI of the brain is the basic diagnostic test for MS. Lesions are located in the white matter and tend to be close to the ventricles. In addition to a positive MRI, confirmation of the diagnosis requires a history of at least two clinical attacks and immunoglobulin changes (oligoclonal bands or elevated IgG levels) in the CSF. This patient met all three criteria.

Initial Treatment

Steroids remain the first-line treatment for new-onset MS. However, steroid administration is very different in patients with MS than in those with many other diseases. Very high doses are customary—typically, a gram of methylprednisolone is given intravenously every day for three or five days.

Patient and family education is critically important in MS. Because it is a lifelong disorder, patients should be encouraged to become as well-informed as possible about the disease. Physicians often do not have the needed information or the time to give it, so other health professionals play a valuable role in this respect. In medical centers that provide comprehensive MS care, specially trained nurses generally assume responsibility for this task.

The Internet can be both a useful and misleading educational resource for MS. There is a great deal of misinformation online, so I recommend Web sites such as that of the National Multiple Sclerosis Society, which is careful about the information it provides.

As occurs with many chronic illnesses, MS patients are often attracted to alternative or complementary medicine. A majority of MS patients try an alternative modality, such as acupuncture, herbal therapy, or hippotherapy (a type of therapy involving horseback riding). Unfortunately, claims of efficacy about many of these modalities are often based on anecdotal evidence. I do not object to patients trying these treatments, provided they are not dangerous, but they should not replace agents that have been tested in placebo-controlled trials and shown to work.

Case 1: Immunomodulatory Therapy

The patient was started on subcutaneous glatiramer, 20 mg a day. She was counseled on diet and exercise.

The National Multiple Sclerosis Society, through its medical advisory board, recommends that patients with newly diagnosed MS be started as soon as possible on one of the recently developed immunomodulating drugs. Two drugs have been approved by the Food and Drug...
Administration (FDA) for this stage of disease. One is beta-interferon, two forms of which--1a and 1b--are available from different pharmaceutical companies; the other is glatiramer.

Which drug to choose is a complex decision. One consideration is patient convenience. All three drugs are injected, but on a different schedule: beta-la-interferon is given once a week intramuscularly, beta-lb-interferon is given every other day subcutaneously, and glatiramer is given every day subcutaneously.

Because the three agents were studied in somewhat different protocols, it is not clear which is most efficacious. In my practice, however, the evidence is strongest for glatiramer. It appears to better reduce the number of relapses and retard the development of permanent disability over the long-term.

A third consideration is patient tolerance. The beta-interferons tend to have many side effects: flulike symptoms (including fever and chills), increased fatigue, and with beta-lb-interferon, frequent injection site reactions, which may last for several weeks. Severe site reactions, which occur in about 5% of patients, may progress to skin breakdown and necrosis. Depression and suicidal ideation may be a side effect of the interferons; however, this is hard to measure in patients with MS because the disease itself usually produces depression. The interferons may result in menstrual abnormalities, and there is some concern that they may induce abortion, so they are not recommended during pregnancy. Moreover, the interferons are FDA Pregnancy Category C agents--the risk of teratogenicity cannot be ruled out.

The skin reactions associated with glatiramer last only about 12 hours and do not lead to dermal breakdown, so they are not as cosmetically important as the beta-interferon reactions. Glatiramer does not cause flulike symptoms and has no effect menstruation. It is a Pregnancy Category B agent (no evidence of teratogenic risk in humans); nevertheless, it too is not recommended during pregnancy.

A peculiar side effect of glatiramer is called immediate postinjection reaction. Right after the injection, the patient experiences facial flushing, heart palpitations, and chest tightening or even chest pain. The symptoms last from 30 seconds to 30 minutes. Their pathogenesis is not understood, but they are benign; there are no reports of patients having any adverse cardiac effects or long-term sequelae. Even so, patients often react with alarm when they first experience this reaction.

Immediate postinjection reactions occur in about 15% of patients. They never occur during the first few months of therapy and never occur twice in a row, but some patients may have as many as six or seven of them over the course of several years.

Patients who are receiving glatiramer should be instructed about these reactions, so that if one does occur it will be less frightening. On the other hand, they also need to understand that if they have chest discomfort that is not related temporally to the injection, they should not dismiss it as a drug reaction, because MS patients--especially older ones--can have myocardial infarctions or other cardiac disorders.
On balance, glatiramer is much better tolerated than the beta-interferons. My patients who receive the drug show better compliance than do those taking an interferon, because glatiramer is easier to take, despite the greater frequency of injections.

Along with immunomodulatory therapy, MS patients should get involved with activities that maintain general health. In addition to a regular exercise program, physicians should stress the importance of a good diet.

Case 2: Presentation

A 35-year-old man presented to a neurologist for advice on his MS drug regimen. A stockbroker, the patient worked 10 to 12 hours a day and commuted from one coast to another every two weeks.

MS had been diagnosed eight years earlier. At first, the patient had one to two attacks a year, from which he recovered with short courses of intravenous methylprednisolone. Two years ago, he complained of bilateral lower extremity weakness and partial impotence. His sensory level at that time was T10. MRI showed periventricular lesions on T2-weighted images and several black holes on T1 images. Lesions were also visible in the corpus callosum, and mild enlargement of the lateral ventricles was noted.

Treatment was begun with beta-la-interferon, 30 µg a week. No more relapses occurred, but the patient had been unable to jog and gradually cut down his exercise to walking three to five blocks.

More recently, the patient needed an electronic personal organizer to keep track of client names and appointments. He also had some urinary urgency and two episodes of incontinence. He was concerned about the development of neutralizing antibodies to interferon and wanted an opinion on alternative medication.

This case is representative of secondary, progressive MS. In the early stages, most patients have relapsing-remitting disease, which is characterized by periodic attacks with complete, or relatively complete, recovery between episodes. After about 10 years, the pattern tends to change; acute relapses become less common or stop completely, but patients experience a progressive neurologic decline, with steadily increasing disability.

This patient’s exacerbation two years ago heralded the beginning of the progressive stage. Impairment of ambulation, urinary and sexual function, and finally cognitive function are characteristic of this stage. Short-term memory loss may force patients to use mechanical aids. Over time, memory loss becomes severe enough to affect employment, interpersonal relationships, and family roles.

This patient’s MRI showed the lesions typical of the progressive stage.
MRI T2 images tend to be a composite of all the abnormalities that occur in the brain, including acute changes like edema and more chronic changes like demyelination and axonal damage. Lesions on the T1 image—the so-called black holes—are most closely associated with clinical neurologic disability and are considered the most destructive long-term lesions. Although not done in this patient, my colleagues and I often ask for the contrast medium gadolinium when ordering MRI scans in MS patients, since it is taken up preferentially in active lesions.

Mild enlargement of the lateral ventricles is typical in patients with established MS. Brain atrophy is now a recognized aspect of the disease; it becomes increasingly prominent over time.

Case 2: Treatment Adjusted

Laboratory testing showed high titers of neutralizing antibodies to beta-1a-interferon. Interferon therapy was discontinued. After a discussion of risks and benefits, the patient agreed to treatment with mitoxantrone.

This patient's continued deterioration despite immunomodulating therapy suggested that interferon therapy had failed. The first step in such cases is to check for the development of neutralizing antibodies to the interferon. There is evidence that patients with persistent high titers of neutralizing antibodies lose the clinical effect of the interferon. Testing for antibodies is available in commercial laboratories, and one of the companies that makes interferon offers it at no charge.

Unfortunately, because antibodies to one interferon cross-react with the other interferon, it is probably of no value to switch from one interferon to another. Switching from interferon to glatiramer is an option, but there are no controlled studies about the use of this agent in patients with progressive MS. Patients enrolled in the glatiramer studies have now been followed for six years, and the majority of them remain in stable condition; however, these patients entered the trials with relapsing-remitting rather than progressive disease.

The other option is mitoxantrone, an immunosuppressive agent with a long history of use in cancer patients that received FDA approval as an MS treatment late last year. Mitoxantrone is not a cure, but it has been shown to produce significant stabilization of progressive MS in a significant percentage of patients, compared with placebo.

As MS therapy, mitoxantrone is given intravenously once every three months, which of course is very convenient for patients. Acute side effects are few—some hair loss and nausea for a day or two after the infusion.

The problem with mitoxantrone is that it eventually causes myocardial damage. The risk is cumulative; at a total dose of about 125 mg/m2—which MS patients reach after about 2.5 years of treatment—the danger of cardiac damage and heart failure becomes too great and the agent must be discontinued.

In the past, a number of other immunosuppressive drugs, most notably
Cyclophosphamide and azathioprine have been used in patients with progressive MS. These agents remain options, although they have never received FDA approval for the treatment of MS.

Case 3: Presentation

A 43-year-old woman presented to a neurologist for treatment. Ten years earlier, diplopia had developed, and her primary care physician had diagnosed bilateral intranuclear ophthalmoplegia. She had not been evaluated by a neurologist at the time, because there was not one available in the small town where she lived. Her symptoms resolved, except for blurred vision in warm weather. She was also troubled by fatigue.

Five years later, she began to have trouble walking and started using a cane. Spastic paraparesis gradually developed, and one year ago, she began to use a walker. She had had no further relapses. Her local physician did not recommend any therapy.

One week before her visit to the neurologist, a brain MRI revealed multiple lesions on T2-weighted images in the cerebral white matter and brain stem, several of which enhanced with gadolinium.

The patient was started on immunomodulatory therapy with glatiramer. In addition, amantadine was prescribed for her fatigue and baclofen titration was begun for the spastic paresis. She was referred to a physical therapist.

This case illustrates the disparity in the quality of MS care in the United States. At one end of the spectrum is the patient such as this one, who lives in a rural area far away from a neurologist and whose primary care physician is not especially knowledgeable about or interested in MS. At the other is the big-city patient who receives care at an MS center.

The latter represents the ideal, of course. MS is a complex, difficult disease that requires a comprehensive approach to management. In addition to the diagnosing/treating physician, the management team at such a center includes physical and occupational therapists, MS nurses, social workers, and sometimes psychologists, as well as other medical specialists such as urologists, ophthalmologists, and physiatrists. MS therapy is a rapidly changing field, and the members of these teams are much more likely to be conversant with the latest developments.

This patient’s clinical course was in many respects typical. Heat intolerance is seen with other neurologic disorders but is especially notable in MS patients. Increased body temperature for any reason—exercise, fever, a hot bath—brings out latent neurologic symptoms. The symptoms resolve if the patient can cool off, for example, by moving to an air-conditioned space or immersing in a swimming pool.
Fatigue is an almost universal component of MS and is a very disabling feature of the disorder. Indeed, it may be sufficiently severe to justify application for disability benefits. I tell patients that when their disease becomes more active, fatigue is more likely to be felt. Short periods of rest can be helpful when the fatigue becomes overwhelming. I also inform family members and employers that although the fatigue is not as obvious as other symptoms, such as impaired walking, it may nevertheless be just as disabling.

There are some drugs that help to reduce fatigue; the most important of these is the anti-influenza agent amantadine. A new drug, modafinil, is also beneficial, as are some of the selective serotonin reuptake inhibitors (SSRIs). The SSRIs are usually prescribed at low dosages; fluoxetine, for example is given at 5 mg a day.

When patients encounter movement difficulties, such as impaired walking, they are referred to a physical therapist for evaluation. Monthly physical therapy sessions can be very helpful, as can an exercise and stretching program. However, it is vital that the therapist be interested in and knowledgeable of MS. Unfortunately, many physical therapists are trained to care for episodic conditions such as stroke or head injury and do not understand the chronic yet constantly changing nature of MS.

Physical therapists can also ensure that patients are supplied with the appropriate assistive devices. For example, many MS patients with impaired ambulation will benefit from one of the newer wheeled walkers, which provide both security and enhance ambulation. Walker-assisted activities such as going the mall or church are important for patients' psychological well-being.

The antispasmodic medication most commonly used in patients with MS is baclofen; indeed, it is taken by almost every MS patient with disabling progressive disease. Titration is critical with this drug because the effective dose varies widely; some patients do well with 30 mg a day, others need as much as 120 mg a day.

The antispasmodic tizanidine is fairly effective for MS-associated spasticity but tends to produce considerable drowsiness, which makes it less useful during the day. Diazepam, especially when used in small doses (e.g., 2-5 mg/day) in conjunction with baclofen, can be quite useful in helping to reduce spasticity.

Patients with severe spasticity often benefit from a baclofen pump. The subcutaneously implanted reservoir is attached to a catheter that inserts directly into the subarachnoid space, permitting the infusion of very small, carefully regulated doses into the CSF and thereby maximizing efficacy and minimizing side effects.

Beyond symptomatic therapy, what can be done in a case like this? Again, the patient has progressive disease, and treatment should begin with an immunomodulating agent—one of the interferons or glatiramer. Granted, the use of immunomodulating agents has not been well studied in patients with progressive disease; indeed, some studies have shown conflicting results. For example, beta-1b-interferon showed a significant beneficial effect in a European trial but not in a similarly designed U. S. trial. Glatiramer, however, in a trial of more than 208 patients, reduced the
progression of disability during six years of followup. Thus, I usually attempt a trial with glatiramer before opting for immunosuppressive therapy.

It takes six months to a year for the full effects of immunomodulating agents to become apparent, so I like patients to start therapy as soon as possible and then return at three-month intervals for evaluation of disability. If disability does not stabilize within six months to a year, the patient should be considered for treatment with mitoxantrone or another immunosuppressive agent.

Commentary

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Johnson has based his discussion on three cases of multiple sclerosis that presented with fairly common clinical scenarios—the first with classic exacerbating and remitting disease and the other two with relapsing-remitting disease that evolved to secondarily progressive disease.

Early on, Johnson makes the point that a diagnosis of MS needs to be confirmed by examination of the cerebrospinal fluid. I agree fully. MRI is often the initial investigation in patients with presumed MS; however, I have seen a number of patients in whom a diagnosis of MS was made erroneously after MRI showed small lesions in the white matter; these patients had another disease, inexplicable symptoms, or a conversion reaction. Even experienced neuroradiologists have a tendency to suggest the diagnosis of MS with varying degrees of confidence solely on the basis of MRI findings.

The diagnosis of MS is a clinical one that should be arrived at only after careful review of the patient's history, physical examination, the MRI findings (with consideration of the extent to which the lesions are typical of MS), and examination of the lumbar puncture (to look for oligoclonal bands as well as abnormalities suggestive of other disorders). With respect to case 2, for example, one must keep in mind that although the development of paraparesis with spinal sensory level (i.e., loss of sensation below a sequential spinal level, indicative of a localized cord spinal lesion) is common in MS, a similar clinical picture may result from spinal cord compression by meningioma, a common tumor in women. Partial response to steroid therapy may occur in patients with tumor-induced compression; thus, I would suggest that MRI of the spine be performed whenever the clinical picture warrants.

Expert consensus has concluded that the three immunomodulatory drugs approved for the treatment of MS provide sufficient benefit (i.e., in terms of reducing attack frequency and delaying secondary progression) to justify their initiation when the diagnosis is first confirmed, rather than waiting for disease exacerbations. The expense, inconvenience, and side effects of the drugs mandate that one be secure about the diagnosis.

Although glatiramer is widely used to treat MS and generally produces milder injection site reactions than do the beta-interferons, it should be
remembered that glatiramer therapy is not guaranteed to be free of skin reactions, and in my experience, some of them may persist. In addition, many patients prefer once-weekly administration of beta-la-interferon to daily injections of glatiramer. A clinical trial of oral glatiramer currently being conducted may demonstrate benefits comparable to those of subcutaneous glatiramer, obviating the necessity for the parental route with its complications and inconvenience.

Like Johnson, I think that exercise is important for patients with MS. Many patients avoid exercise because it causes such severe fatigue or because exercise-induced increases in body temperature cause immediate symptoms or exacerbation of symptoms. The exercise regimen must be carefully tailored to the patient's tolerance level and combined, if necessary, with cooling techniques (e.g., fans, cool towels, air conditioning) that moderate the development of heat-induced symptoms. Unrecognized urinary tract infection is a common cause of increased body temperature in many patients. Daytime fatigue may result from disordered sleep, which, in turn, may be caused by nocturnal cramps or flexor spasms, depression, or frequent trips to the bathroom for voiding.

As mentioned by Johnson, amantadine, modafinil, and fluoxetine can moderate fatigue in some patients. Pemoline is also useful for this purpose; however, both pemoline and fluoxetine should be avoided if the patient has a history of seizures or is taking an MAO inhibitor.

In their search for symptomatic relief, MS patients may turn to alternative medications, diets, and procedures. Some of these treatments may be of dubious benefit. Johnson mentioned several of these. In addition, I have encountered patients who have had all of their dental amalgam fillings replaced or subjected themselves to chelation therapy. Advising patients about the value of alternative treatments is difficult, but it is important to help spare them unnecessary expense, side effects, and dashed hopes. Physicians and patients seeking more information about both successful and unsuccessful MS treatments are advised to consult Therapeutic Claims in Multiple Sclerosis: A Guide to Treatments by William A. Sibley and colleagues.

Selected Reading