Multiple Sclerosis:

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Advances in the understanding of multiple sclerosis (MS) have translated into aggressive treatment regimens that enhance patients' quality of life. In this article, we discuss the therapeutic options, especially treatments that are directed toward the underlying immunologic mechanisms of the disease. Because of its direct effect on quality of life, aggressive management of symptoms is emphasized.

In previous article (CONSULTANT, July 2005, page 844), we described common signs and symptoms of MS as well as the laboratory findings that confirm the diagnosis.

DISEASE MODULATION

Although there is no cure for MS, immunomodulatory agents can decrease the number of neurologic events and slow the progression of disability over time. Clinical trial results show that these drugs, particularly the interferons, reduce the progression of disability.1,2 Because they are "prophylactic" against future disease progression and disability, they should be used early in the course of the disease. We treat all patients in whom we have diagnosed a relapsing form of MS, regardless of the level of disability.

The recognition of the significance of a single neurologic event or clinically isolated syndrome in a patient with MRI evidence of previous demyelination raises the question of how early therapy should be started. Although such patients have not met the stringent criteria for MS, which requires at least 2 neurologic events, studies have shown that intervention at this point can delay the occurrence of a second neurologic event.3,4

The targets of disease modulation are the underlying immunologic mechanisms of MS. Although current agents primarily target the T-cell system, there is increasing interest in the role of the B cell.

Table 1

Agents approved by the FDA for treatment of relapsing-remitting MS include interferon beta-1b, interferon beta-1a (high- and low-dose), and glatiramer acetate.1,5-7 As Table 1 shows, all these drugs reduce the rate of relapse, and some also slow disease progression. In a large European trial, interferon beta-1b also reduced the progression of disability in patients with secondary progressive MS who continued to have superimposed relapses.2

Interferon beta. These agents modulate the disease process by decreasing T-cell replication and by stabilizing the blood-brain barrier, thereby preventing the entry of activated T cells into the CNS. Common adverse effects of the interferon agents include flu-like symptoms and injection site reactions. Premedication and dose titration enhance the tolerability of these agents. Acetaminophen or an NSAID, combined with diphenhydramine, taken 30 minutes before the injection attenuates the flu-like symptoms that frequently accompany therapy. Interferon beta is titrated by starting the drug at one quarter of the full dose for 1 to 2 weeks, then half the dose for 1 to 2 weeks, then three quarters of the dose for another 1 to 2 weeks, then finally the full dose. Injection site reactions are usually localized areas of erythema; necrotic reactions are rare.

An elevation of liver enzyme levels to 2 to 3 times baseline is common. Rarely, interferon therapy must be discontinued because of elevated liver enzyme levels. Although the clinical trials have not shown a clear increase in depression we, as well as other neurologists, have seen depression develop after a patient has started taking an interferon beta
agent. Depression associated with interferon beta may respond to antidepressants. Interferon beta may not be appropriate for patients who have a history of severe depression, especially if there is a history of suicidal ideation. Interferons are rated FDA pregnancy category C because of their potential abortifacient effects.

**Glatiramer acetate.** Although glatiramer is well tolerated and relatively free of side effects, about 5% of injections are associated with a systemic reaction that consists of tachycardia and dyspnea. Monitoring of patients has demonstrated that the reactions are benign; however, failure to warn patients about them may lead to unnecessary emergency department visits. Glatiramer is rated FDA pregnancy category B. However, none of the immunomodulatory agents are recommended during pregnancy; they should be stopped before the patient attempts to conceive.

**Mitoxantrone.** This chemotherapeutic agent is indicated for progressive forms of MS. It is generally reserved for patients who are experiencing rapid loss in functioning. Mitoxantrone is typically dosed intravenously every 3 months. The agent is generally well tolerated except for mild nausea and an expected neutropenia that occurs 2 weeks after infusion. The risk of cardiotoxicity limits its long-term use. Cardiac function is screened before therapy is initiated and prior to each dose.

**Intravenous immunoglobulin.** Based on the results of a trial that demonstrated the efficacy of intravenous immunoglobulin (IVIG), we have given IVIG to some patients who have had steady disease progression.

**Methotrexate.** In view of a clinical trial that showed some preservation of upper extremity function in wheelchair-bound patients with progressive MS, some neurologists prescribe oral methotrexate, 7.5 mg weekly, for patients with progressive MS. This therapy is well tolerated. However, there is gathering evidence that the interferons may also be useful in progressive MS. Therefore, we usually use them first.

**Future therapies.** Several exciting therapeutic options are currently being studied. Natalizumab, a monoclonal antibody to the adhesion receptor on the T lymphocyte, was briefly on the market but was voluntarily recalled after 2 cases of progressive multifocal leukoencephalopathy (PML) were reported. PML is caused by a reactivation of the latent JC virus and has been seen primarily in patients with advanced AIDS.

In the future, management of MS will most likely involve combination therapy. Increasingly, combinations of either interferons or glatiramer with oral immunosuppressant or pulse corticosteroid therapy are being used to boost the effectiveness of current agents.

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**SYMPTOMATIC TREATMENT**

Symptomatic therapy encompasses both responses to new neurologic events and long-term therapy for residual symptoms, such as incontinence related to neurogenic bladder. **Table 2** shows a range of approaches that can help patients who have MS. **SHORT-TERM TREATMENT OF RELAPSES**

When deciding whether to give high-dose corticosteroids during an MS attack, you need to distinguish between attacks that merely represent amplification of preexisting signs and symptoms (pseudo-relapses) and relapses that represent signs and symptoms indicative of involvement of new areas in the CNS. For example, a patient with a long-standing paraparesis who, over the course of a few weeks, has increasing weakness in the legs should probably not be given high-dose corticosteroids. Instead, search for an intercurrent illness, such as a urinary tract infection. Use antipyretic agents liberally in febrile patients because fever may worsen preexisting signs and symptoms of MS. Not all relapses need to be treated; target those that affect function, such as vision or gait.

Based on clinical trials, the consensus is that low-dose oral corticosteroids should be avoided, but that high-dose corticosteroids given early during an MS relapse may be beneficial. Pulse corticosteroid therapy decreases the length and severity of a relapse; however, it does not reduce the risk of another relapse.

In patients who have not received a recent course of corticosteroids, 1 g of intravenous methylprednisolone for 3 to 5 days (depending on the severity of the relapse) may be administered. An oral corticosteroid taper over 11 days is recommended in patients who have received multiple corticosteroid courses within the past year or who are experiencing a severely debilitating relapse. Whenever possible, we prefer to use intravenous methylprednisolone.
At times, intravenous therapy cannot be arranged, such as when a patient calls you over the weekend. In those instances, we give oral dexamethasone, 96 mg/d for 5 days, followed by a dose that is tapered over the next 2 weeks (Table 3).

To minimize common adverse effects of high-dose corticosteroids, such as insomnia and GI distress, we prescribe an H₂ antagonist and a sleep agent. Long-term corticosteroid therapy should be avoided to reduce the risk of such comorbid conditions as diabetes and hypertension.

**REHABILITATION**

The role of rehabilitation in MS has been increasingly defined in the past few years. Although MS is a chronic, progressive disorder, functional gains can be made through aggressive rehabilitation after acute events. Also consider rehabilitation for those patients who are experiencing an insidiously progressive decline in functioning. Aggressive symptom management combined with rehabilitation can improve quality of life and help patients regain their independence.

**COMPLEMENTARY AND ALTERNATIVE MEDICINE**

Surveys have revealed that up to 80% of patients with MS use complementary and alternative medicine, such as high-dose vitamins, bee sting therapy, and marijuana. It is vital to open the lines of communication with patients so that they feel comfortable with disclosing their entire treatment regimen.

**References:**


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