Management of patients receiving interferon beta-1b for multiple sclerosis:

Report of a consensus conference*

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Article abstract—Results of a double-blind, placebo-controlled study in ambulatory patients with relapsing-remitting MS showed that interferon beta-1b reduced the rate of exacerbations by one-third compared with placebo and limited new disease activity in the brain as evidenced by MRI. Interferon beta-1b, administered subcutaneously at a dosage of 0.25 mg (8 million IU) every other day is indicated for the treatment of ambulatory patients with relapsing-remitting MS. Interferon beta-1b may help a wider range of patients, but it should be prescribed only for patients with a diagnosis of clinically definite or laboratory-supported definite MS. The decision to treat a patient with interferon beta-1b should be individualized; that is, based on each patient’s clinical presentation and course of MS. The most common adverse effects include (1) injection-site reactions and (2) flu-like symptoms, which are generally manageable and usually abate after the first few months of treatment. Spasticity may increase. Patients with severe depression or suicidal ideation should be monitored carefully, and symptomatic treatment should be pursued. Interferon beta-1b is contraindicated in pregant and nursing women. Interferon beta-1b is effective in reducing the progression of total disease burden as seen on MRI in patients with MS. Its use is relatively straightforward and generally does not require alteration in the symptomatic treatment of MS. Patient education and support remain the mainstays of maintaining compliance through the early phases of therapy.

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In July 1993, the Food and Drug Administration (FDA) approved Interferon beta-1b (Betaseron, Berlex Laboratories, Richmond, CA) for the treatment of ambulatory patients with relapsing-remitting MS, based on the results of a double-blind, placebo-controlled, multicenter study that showed that interferon beta-1b reduced the exacerbation rate by 31% compared with placebo and decreased MS activity in the brain as evidenced by MRI. However, during the first 3 years of the study, the impact of interferon beta-1b on disability scores did not reach statistical significance.

This pivotal trial included ambulatory patients with MS, aged 18 to 50 years, with (1) a relapsing-remitting disease course; (2) clinically definite or laboratory-supported definite MS; (3) Kurtzke expanded disability status scale (EDSS) scores of ≤5.5; and (4) evidence of disease activity characterized by at least two acute exacerbations in the previous 2 years. Patients received treatment with 0.05 mg (1.6 million IU) interferon beta-1b, 0.25 mg (8 million IU) interferon beta-1b, or placebo, self-administered subcutaneously every other day.

Based on expert opinion, the Quality Standards Subcommittee of the American Academy of Neurology issued a practice advisory that broadened the treatment recommendations. The consensus was, “If the drug is effective in reducing the number and severity of exacerbations, as shown in the one class 1 study on which FDA approval was based, then any MS patient who experienced true exacerbations should be able to receive the drug.” This includes (1) patients older than age 50; (2) patients with relapsing-progressive disease; and (3) nonambulatory patients (EDSS ≥6.0).

The recent approval of interferon beta-1b, as well as its initially short supply, has resulted in limited experience with the drug. In this paper, we review

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various aspects of interferon beta-1b treatment of patients with MS on the basis of our experience with the agent, either as principal investigators of the Interferon beta-1b (IFNB) Multiple Sclerosis Study Group or during the postapproval marketing period, or both. We discuss the role of interferon beta-1b in the management of MS, including criteria for patient selection, differentiation between symptoms of disease and therapy, prevention and management of drug-related symptoms, and management of exacerbations.

**Selection of patients for therapy with interferon beta-1b.** Only those patients with a diagnosis of clinically definite or laboratory-supported definite MS should receive therapy with interferon beta-1b. Because many initial attacks of MS may go undiagnosed, it is important to take a careful history. The decision to treat patients with interferon beta-1b should be individualized, based on each patient's clinical presentation and disease course.

**Appropriate candidates for interferon beta-1b.** Interferon beta-1b therapy is indicated for patients with relapsing-remitting MS and is also warranted for patients with relapsing-progressive MS who show signs of active disease. Attacks occurring within the previous 2 years indicate probable disease activity, as do gadolinium-enhanced lesions on MRI.

In patients with chronic-progressive disease, overt disease progression may not be clinically apparent but is frequently noted on MRI. As patients reach a more progressive stage, subtle physical or cognitive deterioration is not always easily discernible.

The safety and efficacy of interferon beta-1b have not been evaluated in patients with chronic-progressive disease. However, there is no evidence of a biologic difference between relapsing-remitting disease and secondary progressive disease. Treatment with interferon beta-1b usually is not recommended for patients with secondary progressive disease, unless patients have relapses superimposed on a progressive course.

**Inappropriate candidates for interferon beta-1b.** Interferon beta-1b should not be prescribed for patients with primary progressive disease until there is evidence of a clinical benefit of this agent in progressive disease. Primary progressive disease is characterized by a progressive course from the onset, without any clear-cut relapses throughout the course of the disease. Patients with primary progressive MS predominantly have spinal cord disease with less cerebral involvement and tend to show fewer abnormalities on cranial MRI than do patients with secondary progressive disease. To date, there is no evidence that interferon beta-1b therapy is beneficial in these patients. Primary progressive MS may have a different pathogenesis from relapsing-remitting MS.

Interferon beta-1b should not be considered for patients with mild disease that is characterized by one or two sensory attacks over the course of many years, since it is unlikely that treatment would offer a benefit to such patients. Similarly, interferon beta-1b should not be prescribed for patients with clinically definite MS who have experienced prolonged periods of remission and in whom MRI and clinical examination show no evidence of active disease.

Whether to treat patients who have experienced only one attack in the previous year or who do not have clear-cut relapsing-remitting disease is less clear. The decision to treat involves a combination of clinical history and examination, MRI data, and clinical judgment. The patient, as well as the patient's family, when appropriate, should be involved in the decision-making process. For example, patients who have cervical spinal cord disease, evidence of extensive disease on a brain MRI scan, and clear clinical evidence of an exacerbation resulting in neurologic damage may be considered candidates for therapy, even if they have experienced only one attack in the previous year. However, not all patients who present with spinal cord symptoms have abnormal brain MRI scans. It is not yet known whether there is any prognostic difference between patients whose brain MRI scans are abnormal at that stage and those whose brain MRI findings are normal. In patients who have no evidence of active disease, it may be judicious to obtain another MRI a few months later to look for ongoing activity. At that point, evidence of disease activity would warrant consideration of therapy.

Therefore, for patients who have experienced only one recent attack early in the course of disease, there are two options: (1) Wait for a second exacerbation before starting therapy with interferon beta-1b, or (2) compare a recent MRI scan with one performed 3 to 6 months earlier. If the second option is chosen, the presence of active lesions on the most recent MRI scan, which suggests disease activity, warrants consideration of therapy with interferon beta-1b, even in the absence of significant symptoms. However, as the interval since the acute exacerbation lengthens, there should be less reliance on the MRI findings and more reliance on the clinical examination findings.

Cranial MRI may be used to gauge disease activity, because it may show subclinical ("silent") lesions. Evidence is accumulating that the degree of disease activity, as measured by MRI, correlates with neurologic impairment and that MRI has predictive value as to the course of disease. Progression on MRI provides further evidence of disease activity and may sway the decision-making process in favor of treatment.

**Contraindications to interferon beta-1b.** The only absolute contraindications to the use of interferon beta-1b at this time are (1) hypersensitivity to any component of the product, (2) active, severe depression, and (3) pregnant or nursing women and those who are actively attempting to become pregnant.
Depression. Because depression and suicide are relatively common in patients with MS, a history of depression is not an absolute contraindication to the use of interferon beta-1b. It remains to be determined whether depression or the frequency of suicide attempts are exacerbated by interferon beta-1b therapy. The frequency of depression during the clinical trial with interferon beta-1b was equivalent between the treatment groups (both high and low dose) and the placebo group. Prudence is required, however, because one suicide and four attempted suicides were observed among the patients treated with interferon beta-1b during the clinical trial.1,7

Therapy may be inappropriate in individuals who have a history of suicide attempts or who have major depressive ideation requiring psychiatric intervention or admission to an institution. Under such circumstances, the consideration of interferon beta-1b therapy may be undertaken in conjunction with the patient’s psychiatrist.

Interferon beta-1b therapy may be considered (1) in patients who have a history of depression but who are not currently depressed and (2) in mildly depressed patients. In either circumstance, however, therapy should be considered only for those patients who have a good support system, i.e., family members or caretakers who are able to monitor the patient carefully and be observant for changes in the patient’s behavior, mood, or affect.

When treatment is started, recurrence or worsening of depression, despite appropriate use of antidepressant therapy and other psychotherapeutic interventions, strongly suggests discontinuance of interferon beta-1b. Temporary discontinuance of therapy may be of some value in patients who experience depression while taking interferon beta-1b. It may allow the patient and the physician to determine whether the depression represents a side effect of the medication.

Pregnancy and breast-feeding. There are no adequate, well-controlled studies of the use of interferon beta-1b in pregnant women, but spontaneous abortions have occurred. Thus, therapy should be discontinued in patients who become pregnant while taking the drug.7 Patients need to be counseled not to become pregnant if they are going to start interferon beta-1b therapy and to delay use of the drug until they have completed their family. It is not known whether interferon beta-1b is excreted in human milk. It may be preferable for women to start (or restart) the medication as soon as possible after delivery or after weaning in an attempt to reduce the increased risk of exacerbations associated with the postpartum period.8

Distinguishing between symptoms of disease and therapy. Clinical trial data demonstrate that, compared with placebo, 0.05 mg (1.6 million IU) and 0.25 mg (8 million IU) interferon beta-1b every other day reduced the attack frequency beginning 2 months after treatment onset; however, identical exacerbation rates were observed during the first 2 months after the initiation of therapy.1 Some of the neurologic symptoms reported during this early stage of treatment may result from transient pseudoexacerbations (produced either by clinical or subclinical elevations of temperature or increased spasticity) or from changes in the immune system caused by the immunomodulating effects of interferon beta-1b.

Symptoms related to the use of interferon beta-1b include fever, chills, malaise, muscle aches, and fatigue. Because fatigue and lassitude are common manifestations of MS, they may represent an early reaction to interferon beta-1b treatment or be related to the underlying neurologic disease process. Clinical judgment is needed to distinguish between these possibilities. Decisions are based on the history and severity of symptoms and their temporal profile. Symptoms attributed to interferon beta-1b usually occur early after the initiation of therapy (after the first two or three injections) and frequently abate between injections.

Thus, it is not uncommon for patients to feel worse right after starting therapy or to experience a mild worsening of their symptoms before gradually stabilizing. Spasticity may worsen in some patients. Some patients feel worse the day after an interferon beta-1b injection and then feel relatively better the next day.

Drug interactions between interferon beta-1b and other medications routinely used in the symptomatic treatment of patients with MS have not been reported to date. Therefore, symptomatic therapy for MS usually does not have to be altered when patients receive interferon beta-1b. In addition, patients can generally be effectively managed with the same antidepressant medications and psychotherapeutic interventions that are used for patients with depression who are not receiving interferon beta-1b therapy. Patients who are receiving medications that may alter bone marrow function or that are potentially hepatotoxic should be monitored carefully, however.

Patients should be made aware of the potential effects of initiating treatment and that a temporary worsening of symptoms is not an indication of treatment failure. Patients should understand that therapies they have used for their other symptoms can be continued safely. Education remains an important factor in maintaining compliance through the early phases of therapy.

Prevention and management of symptoms related to therapy. Clinical trial data indicate that interferon beta-1b is well tolerated, with an acceptable risk of adverse experiences.1 The most common symptoms related to therapy with interferon beta-1b, in addition to flu-like symptoms, are local reactions and minor pain at the injection sites.

Flu-like symptoms. The flu-like symptoms (fever, chills, myalgia, headache, and malaise) that follow the introduction of interferon beta-1b remain a com
Local reactions. Injection-site reactions are common and do not appear to be related to body weight. Five types of reactions have been observed: (1) local redness; (2) bruising and pain (unrelated to redness), most commonly related to injection technique; (3) cutaneous or subcutaneous infection, also likely related to injection technique; (4) subcutaneous atrophy; and (5) necrosis, although rare, characterized by small, painful necrotic lesions that become secondarily infected.

Postapproval marketing experience indicates that local reactions are usually less severe when injections are administered over the buttock area; in addition, some patients have reported injections to be more painful over the arms and abdominal area.5

Injection technique should be reviewed periodically with patients to ensure proper depth of injection and rotation of injection sites. Interferon beta-1b therapy may need to be withdrawn and appropriate surgical management (i.e., debridement) instituted in patients who develop multiple necrotic skin lesions.

Other symptoms. No adverse changes in mental status or cognition have been reported in association with use of interferon beta-1b. No increase in the frequency of seizures has been appreciated, and the drug does not appear to lower the seizure threshold. Depression can usually be managed effectively with antidepressant agents and other psychotherapeutic interventions. In patients with MS, selective serotonin reuptake inhibitors appear to be more energizing and to cause less fatigue than traditional tricyclic antidepressants.

In the clinical trial, interferon beta-1b elicited the production of neutralizing antibodies in some patients. A relationship between neutralizing activity and relapse rate is suggested.5 With the exception of a possible flare of psoriasis, no worsening of other autoimmune diseases has been noted.

Management of abnormal laboratory findings. Laboratory values, including a complete blood count (CBC) with platelet count and a chemical profile with emphasis on liver function tests (bilirubin, serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], gamma-glutamyl transeptidase [GGT], alkaline phosphatase), should be obtained before initiating therapy and monitored during the course of treatment (after 4 to 6 weeks, at 12 weeks, and every 12 weeks thereafter). Although most laboratory test abnormalities do not appear to necessitate modification of management, continued monitoring of laboratory studies is recommended, since the long-term consequences of therapy are unknown. Attention must be paid to the possibility that hitherto unknown side effects may surface once the drug is widely used. Patients receiving other medications that can affect bone marrow or liver function, such as anticonvulsants, may require more frequent monitoring.

Findings on CBC. Mild anemia and leukopenia

<table>
<thead>
<tr>
<th>Table</th>
<th>Adverse effects occurring in 69 patients (25 men, 44 women) treated with interferon beta-1b at the Jefferson Medical College of Thomas Jefferson University</th>
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<tbody>
<tr>
<td></td>
<td><strong>Men (%)</strong></td>
</tr>
<tr>
<td>Chills</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (32)</td>
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<tr>
<td>Muscle aches</td>
<td>10 (40)</td>
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<tr>
<td>Fatigue</td>
<td>10 (40)</td>
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<tr>
<td>Weakness</td>
<td>8 (32)</td>
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<tr>
<td>Redness at injection site</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (20)</td>
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<tr>
<td>Increased spasticity</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Siffness</td>
<td>2 (8)</td>
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<tr>
<td>Nausea/vomiting</td>
<td>2 (8)</td>
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<tr>
<td>Sweat</td>
<td>0 (0)</td>
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<tr>
<td>Insomnia</td>
<td>3 (12)</td>
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<tr>
<td>Vertigo/lightheaded</td>
<td>2 (8)</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Palpitations/chest tightness</td>
<td>1 (4)</td>
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<td>Soreness at injection site</td>
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<tr>
<td>Joint and bone pain</td>
<td>0 (0)</td>
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<tr>
<td>Elevated liver enzyme levels</td>
<td>0 (0)</td>
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<tr>
<td>No adverse effects</td>
<td>2 (8)</td>
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mon problem, particularly early after the institution of therapy. However, these symptoms are usually manageable with simple analgesics, such as acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs such as ibuprofen.5 Patients should be advised to take a mild antipyretic/analgesic (e.g., acetaminophen) 4 hours before injection, at the time of injection, and 4 hours after injection; administration of interferon beta-1b at bedtime may also permit patients to sleep through their symptoms. Flulike symptoms generally resolve within a few months of institution of therapy.

Relationship to body weight. There is some indication that the flulike reactions may be directly related to body weight in relationship to the fixed dose that is recommended for treatment. In 69 men and women treated with interferon beta-1b at the Jefferson Medical College of Thomas Jefferson University, Philadelphia, the frequency of flulike symptoms (chills and fever) appears to be greater in women than in men (table), suggesting the influence of body weight on tolerance to therapy.

The recommended starting dose is 0.25 mg (8 million IU) every other day.7 However, patients who experience severe, intolerable flulike symptoms may benefit from a temporary reduction in dose. Starting therapy at half the recommended dose for the first 2 to 4 weeks has reduced the incidence of flulike symptoms in some patients (A.E.M., B.H.E., unpublished data, 1994).
are common findings, which generally do not necessitate treatment discontinuation. White blood cell counts, which may occasionally dip below 3,000 cells/mm³, usually rebound and stabilize. There are no known instances of opportunistic infection. Thrombocytopenia occurring late in the course of treatment has been observed rarely.

**Findings on liver function tests.** In some patients, elevations or fluctuations in either SGPT or SGOT levels have been observed without clinical sequelae. Such fluctuations do not usually require an interruption of therapy. In the clinical trial of interferon beta-1b, therapy was discontinued if hepatic transaminase (SGPT/SGOT) levels exceeded 10 times the upper limit of normal, or if bilirubin levels exceeded five times the upper limit of normal. In each instance during the trial, hepatic enzyme abnormalities returned to normal after discontinuation of therapy. Dose was reduced in two patients because of increased liver enzyme levels, and three patients were discontinued from interferon beta-1b therapy because of abnormal liver enzyme values. Temporar-
dy discontinuation of therapy is recommended when all transferase enzyme levels, as well as alkaline phosphatase and bilirubin levels, are elevated. After these levels normalize, interferon beta-1b can be reintroduced at 25% of the usual dose (i.e., 2 million IU) with a slow buildup of the dose as liver function is monitored. Subsequent chemical liver dysfunction is rare.

**Drug–drug interactions.** No drug–drug interactions have been noted to date. Drugs that have been commonly administered concomitantly with interferon beta-1b include corticosteroids, corticotropin, antidepressants, carbamazepine, phenytoin, baclofen, oxybutynin, and acetaminophen. Concomitant administration of carbamazepine or acetaminophen in high doses, however, may result in elevated liver enzyme levels, requiring careful monitoring.

**Suspension of therapy.** A temporary discontinuation of therapy may be helpful for patients who exhibit depression, abnormal liver function test results, or other symptoms not easily explained. It seems reasonable to interrupt the drug and then restart it at a lower dose. Subsequent reintroduction of therapy is not recommended in patients with (1) depression unresponsive to other management and (2) persisting abnormal liver function test results, with SGPT/SGOT greater than 10 times the upper limit of normal or bilirubin greater than five times the upper limit of normal. There are no known adverse events associated with discontinuation of interferon beta-1b therapy.

**Management of exacerbations in patients receiving interferon beta-1b.** Although treatment with interferon beta-1b reduces the frequency of exacerbations and the severity of attacks that do occur, the drug is not a cure for MS; patients may experience relapses. Before patients are treated for an acute exacerbation, it is important to determine that they are experiencing some functional impairment, since such therapy may have potentially significant adverse effects.

When exacerbations occur, several treatment options are available. Many physicians do not treat mild exacerbations. For more severe attacks, the drug most commonly used at present is intravenous methylprednisolone, followed by oral prednisone. No uniform opinion exists at present regarding how long to treat an exacerbation and what dose of methyl prednisolone should be given.

**Intravenous and oral corticosteroids.** The Optic Neuritis Study treatment trial conducted by Beck et al demonstrated that patients with isolated acute optic neuritis who received intravenous methylprednisolone (250 mg every 6 hr) for 3 days, followed by oral prednisone (1 mg/kg) for 11 days, had a lower rate of development of clinically definite MS over a 2-year period than did patients who received only oral prednisone (1 mg/kg) for 14 days or placebo for 14 days. Based on the results of this study, most clinicians now treat significant exacerbations with a short course of intravenous methylprednisolone followed by oral prednisone.

**Dosage regimens vary:** Methylprednisolone may be given at 1,000 or 500 mg/day for 5 days (or 3 days in patients with very mild disease) followed by a rapid taper of oral prednisone. Some physicians use other prednisonone-tapering schedules, and some do not prescribe any oral treatment after the course of intravenous methylprednisolone. Currently, no data exist to support one such regimen over another. If a patient first responds to treatment with intravenous methylprednisolone followed by an oral prednisone taper, but then experiences a more extensive exacerbation, the full course of steroid treatment may be repeated; alternatively, the duration of the oral prednisone administration may be extended. If the selected treatment for an acute exacerbation fails, a course of corticosteroid may be considered.

Some physicians try to protect patients from the exacerbations that may occur during the first 2 months of interferon beta-1b treatment by coadministering corticosteroids at the start of therapy; however, no specific steroid dosage or length of administration has been determined.

**Adjunctive therapy.** Analgesics, muscle relaxants, and antibiotics are commonly used as adjunctive treatment of MS. None of these drugs are contraindicated because of treatment with interferon beta-1b or require special precautions, except monitoring of liver function when appropriate.

**Other issues.** Concomitant diabetes does not appear to require different management strategies in patients receiving therapy with interferon beta-1b. Patients appear to tolerate both insulin and other treatments for diabetes in conjunction with interferon beta-1b without any known adverse events. In such patients, however, the use of methylprednisolone requires appropriate monitoring of the diabetes. There is no clinical evidence that interferon...
beta-1b has any adverse effects on wound healing, which is an issue for patients who require hospital admission for an elective surgical procedure or for patients with decubitus or plantar ulcers.

**Patient education.** The nature of interferon beta-1b treatment, the objectives of the treatment, and what is likely to happen during treatment should be clearly stated and freely discussed with patients before therapy is started. Patients should be fully aware of potential side effects— injection-site reactions and flulike symptoms—and how best to manage or perhaps avoid them.

**Injection technique.** At first, many patients may be concerned about their ability to self-administer the injections. Patient education is essential. The first injection should take place in the physician’s office or clinic so that patients can be fully instructed about the appropriate preparation of the drug (solubilizing the lyophilized powder in the diluent) and in the technique of self-injection. Initially, it may be helpful to employ the assistance of a hospital diabetes nurse, who is familiar with the technique of subcutaneous injection and patient instruction. The first three to four injections probably will be the most difficult, both in terms of difficulty of self-injection and side effects.

**Side effects.** Patients are likely to experience some adverse effects of the drug, at least initially, and perhaps for as long as 2 to 3 months, after which time the symptoms usually abate. Many patients may experience redness and minor pain at the injection sites; the local redness may persist for many weeks after a particular injection, although the pain at the injection site seems to bear no relationship to the redness and usually resolves soon after the injection has ended. Giving the injections predominantly in nonexposed areas of the body may alleviate cosmetic concerns. Massaging the injection site helps to disperse the drug, allowing for more rapid absorption and reducing local adverse effects. Injection technique should be reviewed periodically to ensure that sites are properly rotated and injections are given to the proper depth. Occasionally, a patient will develop a significant local effect, which may limit the use of the drug.

Fever usually occurs between 3 and 8 hours after the injection, but it may be delayed for as long as 12 to 18 hours. Patients should be counseled to take an antipyretic/analgesic agent shortly before, and again several hours after, the injection. Some may wish to administer the injection at bedtime, which may lessen the impact of flulike symptoms.

**Exacerbations.** Interferon beta-1b, while not a cure for MS, will help to reduce the frequency and severity of exacerbations. However, exacerbations are to be expected, and they should not be regarded by the patient or the physician as a failure of treatment.

**Patient compliance.** Compliance varies from patient to patient, depending on the patient’s expecta-

tions, motivation, and commitment to therapy. Patient education is critical for reducing unrealistic expectations. Patients may benefit from encouragement during the first few months if systemic side effects are prominent. Patients experiencing an exacerbation may become dismayed, disgruntled, and frustrated, and some of this unhappiness may be directed toward physicians and other caretakers. Under these circumstances, the compliance threshold may decrease, and emotional and medical support may have to be provided. Maintaining open communications with patients is essential to reduce unnecessary discontinuance of treatment.

**Discontinuation of therapy.** Patients who respond to interferon beta-1b—those experiencing fewer exacerbations and tolerating the drug without significant side effects—should be maintained on therapy indefinitely. However, patients not responding well to interferon beta-1b—those experiencing intolerable side effects related to therapy, requiring increased courses of steroids, or showing a clearly progressive decline in EDSS score over the course of a year—should discontinue the drug. An immunosuppressant agent then may be considered. Copolymer 1 (Coxaphone, Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel), once approved by the FDA, may be a viable alternative therapy for patients with relapsing disease and little disability.\textsuperscript{10,11}

Several agents are undergoing investigational use. The future of the treatment of MS will probably involve multiple agents with different mechanisms of action that affect the disease at different stages. Future trials are recommended to investigate the use of interferon beta-1b in combination with other agents.

There is no evidence of a rebound effect in patients who have been followed up over time after stopping therapy, although the number of patients and the duration of followup are still limited. Increased neurologic worsening has been reported after discontinuation of an investigational drug (recombinant interferon alfa-2) in the treatment of MS.\textsuperscript{12} Therefore, it is recommended that therapy with interferon beta-1b be maintained, if possible.

**New technologies in the diagnosis of MS.** Several new technologies have evolved for the diagnosis and management of MS. MRI scanning has emerged as a concomitant indicator of disease and disease activity and is increasingly used as a diagnostic tool.\textsuperscript{2,4,6} Magnetization transfer ratio (MTR) imaging, segmentation analysis, and proton magnetic resonance spectroscopy (MRS) are among the newer technologies that have drawn particular attention.\textsuperscript{13-16} MTR imaging increases the pathologic specificity of MRI, has the potential to differentiate demyelination in MS from less destructive pathologic changes, and may be useful in monitoring changes in tissue brought about by treatment.\textsuperscript{19} Proton MRS can be used to monitor demyelination and axonal loss and offers the possibility of examining acute
changes in choline and possibly other chemicals that will reflect the acute inflammatory changes that occur in tissue affected by MS.\textsuperscript{14,15} Segmentation analysis allows for volumetric assessment of lesion load and helps differentiate between long-term axonal lesions and more edematous lesions that can be followed over time.\textsuperscript{16}

Various laboratory measures have been examined for correlation with the course of MS. CSF myelin basic protein levels correlate with acute demyelination, and levels of urine myelin basic proteinlike material, which is different in form from that in the CSF, appear to correlate with a transition to the progressive phase of disease.\textsuperscript{17} Other ongoing studies include the role of cytokines and cytokine receptors. At present, none of these studies has yielded sufficient data that can be applied to clinical management. Nevertheless, results are encouraging and have potential for further therapeutic advances.

New therapies. Subsequent to this consensus conference, two additional clinical trials in MS reported successful results.\textsuperscript{10,18} A fuller explanation of the role of interferon beta-1a (Avonex, Biogen, Inc., Cambridge, MA) awaits publication in the form of a peer-reviewed manuscript. The other successful trial evaluated copolymer 1, which, when administered subcutaneously on a daily basis, reduced the relapse rate similar to interferon beta-1b.\textsuperscript{10} Other outcome measures, such as percentage of exacerbation-free patients and time to first exacerbation, were less robust than those found with interferon beta-1b.\textsuperscript{10} Copolymer 1 has a more favorable side-effect profile, which should be balanced against the need for daily subcutaneous injection. FDA approval of these new agents will further add to the therapeutic armamentarium of the neurologist treating patients with MS and afford neurologists the opportunity to consider combination therapies.

Management of MS and quality of life. Symptomatic relief and counseling of patients with MS have a strong positive impact on quality of life and must be provided, along with new therapeutic advances in treatment. Many patients who hitherto have not received treatment for MS may now be encouraged to seek treatment because of the availability of new therapies such as interferon beta-1b. When discussing treatments that have the potential to modify the disease course itself, clinicians also have the opportunity to reevaluate patients with MS, to address specific symptomatic and rehabilitation issues, to educate and counsel the family, and to focus treatment on patients as a whole, with the overall goal of improving patients' quality of life.

Summary and conclusions. As the first approved, effective treatment for relapsing-remitting MS, interferon beta-1b signals a new era in the management of MS. Clinicians are now faced with the challenge of integrating interferon beta-1b into their practices and applying clinical experience, much of which has not yet been published in the medical literature. Although interferon beta-1b is a new agent, neurologists should be assured that use of this agent is relatively straightforward and generally does not require alteration of symptomatic treatment. Patients have a greater probability now than in the past of achieving an improved quality of life.

References
2. Paty DW, Li DKB, the UBC MS/MRI Study Group, the IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993;43:662–667.