ABSTRACT

Most patients with multiple sclerosis (MS) initially experience a clinical presentation that has been referred to as relapsing-remitting MS, which is defined by a pattern of acute episodes of impaired neurologic function and a return to normal or near-normal function between episodes. A number of options are available to treat acute MS exacerbations or to reduce the likelihood of future episodes. Steroids, especially intravenous methylprednisolone, have been used to accelerate recovery from acute MS episodes. Two formulations of interferon beta-1a are approved for use in MS—one is administered by intramuscular injection once weekly and one by subcutaneous injection 3 times per week. One formulation of interferon beta-1b is also administered by subcutaneous injection every other day. Glatiramer acetate is also used to prevent MS exacerbations. Randomized, controlled trials have demonstrated improvements in attack frequency and other clinical outcomes with interferon beta preparations and glatiramer acetate. The most common adverse events of MS preventive therapy include flu-like symptoms and injection-site reactions with interferon beta, and injection-site reactions and a postinjection reaction of transient chest pain or tightness with glatiramer acetate.

As described in an accompanying article by Dr Guthrie, most patients with multiple sclerosis (MS) initially present with relapsing-remitting MS (RRMS), which is characterized by acute episodes of MS that are separated by periods of normal or near-normal neurologic function. A number of medications are now available to treat patients with RRMS, including corticosteroids and potentially disease-modifying treatments such as interferon beta and glatiramer acetate.

TREATING ACUTE EXACERBATIONS: STEROIDS

Steroids have long been used to speed the functional recovery of patients with acute MS exacerbations. They are thought to suppress MS exacerbations by decreasing the release of inflammatory cytokines, the activation of T lymphocytes, and the migration of immune cells into the central nervous system (CNS). They may also stimulate the death of these activated immune cells. Methylprednisolone is typically administered at a dose of 1 g/day intravenously (IV), either as a single dose or in divided doses, usually for a total of 3 to 5 days. Some clinicians, but not all, use a gradual taper before discontinuing treatment. Oral prednisone has also been used at very high doses (eg, 1250 mg every other day for 5 days). Typically, adrenocorticotropic hormone has been used only in unusual circumstances (eg, during a methylprednisolone shortage).

PREVENTING EXACERBATIONS: INTERFERONS AND GLATIRAMER ACETATE

Immunomodulatory therapy is a mainstay for the prevention of MS exacerbations. Approved medications include glatiramer acetate and 3 interferon beta formulations—inferferon beta-1a intramuscular (IM), interferon beta-1a subcutaneous (SC), and interferon beta-1b. All of the interferons are assumed to share the
same mechanisms of action in the treatment of MS, which include the preservation of myelin by the suppression of immune cells and inflammatory substances that cause myelin loss.\(^5\)\(^6\) Interferon therapy decreases T-cell activation and secretion of inflammatory cytokines; prevents up-regulation of cell-surface adhesion molecules that are required for activated T cells to enter the CNS; suppresses the formation of tissue-injuring substances (eg, matrix metalloproteases); decreases the proliferation of phagocytic microglia cells, which are thought to damage myelin; and directs the maturation of helper T cells from the inflammatory Th1 type to the anti-inflammatory Th2 type.\(^5\)\(^6\)

In general, the effects of the 2 interferon beta-1a products in MS treatment are similar. Compared with placebo, both have been shown to decrease the frequency of exacerbations and the number of brain lesions visible on magnetic resonance imaging (MRI), and to increase the time before progression of disability (Figure 1).\(^7\)\(^11\) Interferon beta-1a is absorbed more slowly after IM injection than SC injection. Interferon beta-1a IM is administered at a dose of 30 µg once weekly, whereas interferon beta-1a SC is administered at a dose of 44 µg 3 times per week. Both products produce similar adverse effects, including flu-like symptoms and injection-site reactions. Less common effects include laboratory abnormalities (eg, decreased white blood cell count and elevated liver function tests), menstrual abnormalities, and depressed mood. More serious, but rare, adverse effects include hepatic failure and depression of all peripheral blood cell lines; for this reason, liver function tests and a complete blood count are recommended at 1, 3, and 6 months after starting therapy, then periodically thereafter.\(^15\) Randomized clinical trials have shown that early administration of interferon beta-1a, in both IM and SC formulations, beginning after the first clinical attack, slows the progression of MS (Figure 2).\(^13\)\(^15\)

Analyses of different patient subgroups revealed that patients who were the most likely to benefit from early interferon beta-1a therapy were those with the following characteristics: immunoglobulin G synthesis or oligoclonal bands in cerebrospinal fluid samples, 2 or more lesions on MRI, or symptoms that remained 2 months after their initial attack.\(^15\)

Interferon beta-1b is similar to interferon beta-1a in its mechanisms of action and efficacy. It has been shown to reduce the frequency and severity of MS exacerbations compared to placebo, and has also been shown to improve symptoms in patients with secondary progressive multiple sclerosis.\(^16\)\(^17\) It is rapidly absorbed after SC injection, reaching a peak plasma concentration within 1 to 8 hours. Interferon beta-1b produces adverse events that are similar to the adverse events produced by interferon beta-1a, with flu-like symptoms and injection-site reactions occurring most often. The frequency of injection-site reactions for all of the subcutaneous products may be reduced by administering injections to the buttocks instead of the stomach, abdomen, or back of the arm; by using topical hydrocortisone cream 30 minutes before injection; rotating injection sites; and the application of ice or heat.\(^18\)\(^19\) Patients should be counseled that flu-like symptoms usually remit after 2 to 3 months of treatment, and that symptoms may be prevented by using gradual dose increases and the use of acetaminophen or ibuprofen.

A significant obstacle to the long-term efficacy of beta interferons is the formation of neutralizing antibodies (NABs). NABs usually appear after 12 to 18 months, and are more common with interferon beta-
Interferon beta-1b was associated with a small but significantly lower rate of relapse (0.5 vs 0.7 per year). Interferon beta-1b was also associated with fewer new lesions on MRI, but a higher incidence of NABs (22% vs 6% of patients). The EVIDENCE (Evidence of Interferon Dose-Response: European North American Comparative Efficacy) trial was a randomized, open-label study of 677 patients who were treated with interferon beta-1a SC or interferon beta-1a IM for 48 weeks. Relapse rates and the number of active lesions on MRI were lower with the more frequent SC dosing regimen, and the number of patients with NABs was also greater. In an open-label extension phase, patients were allowed to switch to SC dosing, which resulted in a 50% relative reduction in relapse rate during the extension period. An open-label, nonrandomized study in which 156 patients were assigned to whichever

**Comparative Studies**

A small number of clinical studies have directly compared the efficacy of the different agents in patients with RRMS, although none has used a prospective, randomized, double-blind design. The INCOMIN (Independent Comparison of Interferon) study was an open-label comparison of interferon beta-1a IM versus interferon beta-1b in 188 patients who were treated for 2 years.

In contrast with the interferon beta preparations, glatiramer acetate is thought to act by binding to the major histocompatibility complex class II molecule, preventing antigen presentation and T-cell activation, and directing the maturation of helper T cells from the proinflammatory Th1 type to the anti-inflammatory Th2 type. In patients with RRMS, glatiramer acetate reduces the number of exacerbations compared to placebo (Figure 3). It is administered at a dose of 20 mg (1 mL) SC daily. The most common adverse effects of glatiramer acetate include injection-site reactions and a postinjection reaction of transient chest pain or tightness and shortness of breath, which are often described by patients as similar to a panic attack.

**Figure 2. Early Administration of Interferon Beta-1a**

![Graph showing early administration of interferon beta-1a](image-url)

Early administration of interferon beta-1a intramuscularly after a first episode of multiple sclerosis (MS) delays the progression to clinically definite MS, which requires, by definition, at least 2 episodes that are consistent with central nervous system demyelination. After 3 years, the percentage of patients who progressed to clinically definite MS was significantly lower among patients who received interferon beta-1a than placebo ($P = 0.002$). Reprinted with permission from Jacobs et al. *N Engl J Med.* 2000;343:898-904.

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er treatment they preferred compared interferon beta-1a IM, interferon beta-1b, glatiramer acetate, or no treatment. Compared to untreated patients, the mean number of relapses was significantly lower for patients in the glatiramer acetate and interferon beta-1b groups, but not in the interferon beta-1a group. Finally, an open-label, nonrandomized, retrospective 2-year study examined clinical outcomes for patients who had received no treatment, interferon beta-1a IM, interferon beta-1b SC, interferon beta-1b, or glatiramer acetate. The only statistically significant differences between active treatment groups were a lower number of relapses per year with glatiramer acetate than with the other therapies, and a lower rate of treatment discontinuation.

CONCLUSIONS

A 3-day to 5-day course of IV methylprednisolone is commonly used to treat acute MS exacerbations, and may be discontinued with or without a gradual taper. Options to prevent relapses in patients with RRMS include 3 interferon beta preparations and glatiramer acetate. The typical dosing, route of administration, and common adverse effects of these agents are summarized in the Table. All of these agents have been shown to be superior to placebo in randomized controlled trials, but the different treatments have not been rigorously compared to one another.

DISCUSSION HIGHLIGHTS

Dr Guthrie: What is the clinical significance of NABs? Do the patients who develop NABs have a worse outcome?

Dr Bennett: It is very controversial. The latest consensus statement from the American Academy of Neurology on neutralizing antibodies has not progressed very far from the initial statement in early 2000. High titer antibodies are not likely to go away. Antibodies usually start to appear after approximately 6 months, but they don’t start to cause a clinical effect until roughly 18 to 24 months. It was only in the 4-year PRISM study that the effects of antibodies on clinical outcomes were apparent, and especially from years 3 to 4. With shorter trials, due to the low rate of antibody formation during the first few months, the numbers of patients with clinical events is small, which makes it difficult to detect differences between those with and without NABs. I would say that there is no reason for prospective analysis of antibodies right now for patients with MS. Antibodies should not be assessed unless a patient is not doing well on treat-

Table. Medications to Prevent Multiple Sclerosis Exacerbations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a</td>
<td>30 µg</td>
<td>IM</td>
<td>Weekly</td>
<td>Flu-like symptoms</td>
</tr>
<tr>
<td>Interferon beta-1a</td>
<td>44 µg</td>
<td>SC</td>
<td>3 times per week</td>
<td>Flu-like symptoms, injection-site reactions</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>8 M IU</td>
<td>SC</td>
<td>Every other day</td>
<td>Flu-like symptoms, injection-site reactions</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>20 mg</td>
<td>SC</td>
<td>Daily</td>
<td>Injection-site reactions, chest tightness</td>
</tr>
</tbody>
</table>

Data from Khan et al; Haas and Firzlaff; Avonex (interferon beta-1a) [prescribing information]; Betaseron (interferon beta-1b) [prescribing information]; Copaxone (glatiramer acetate injection) [prescribing information].
Dr Ryan: Some of these antibodies dissipate over time. Suppose that you have a patient who is starting to deteriorate clinically, and antibody testing reveals a high antibody titer. You switch them to glatiramer acetate, but they don’t tolerate it very well. Could you now switch the patient back to interferon? Would you use a different formulation, such as the IM rather than SC formulation of interferon beta-1a?  

Dr Bennett: No one has done that exact experiment. One study enrolled some patients who had developed antibodies in an earlier clinical study of interferon beta-1b and started them on interferon beta-1a. Many of the patients lost their antibody titers with interferon beta-1a over time. So, there is the possibility of losing antibodies even while still continuing to take interferon. This was a very small group of patients. I think that with the release of new agents, such as natalizumab, we have the opportunity in those patients who develop antibodies to go to something else. But obviously, there is a risk-benefit ratio that has to be evaluated with these new drugs. Although it is a real issue, the vast majority of our patients fail interferon therapy in the absence of neutralizing antibodies. I think that the most important pharmacoeconomic issue is that we need to understand what antibodies mean for a patient who is failing to respond. We need to know whether the patient is failing because of the antibodies, or whether the medication itself is ineffective.

REFERENCES

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