The role of glatiramer acetate in the early treatment of multiple sclerosis

David W Brandes
Hope MS Center, Knoxville, TN, USA; UCLA, Los Angeles, CA, USA

Abstract: The treatment of the underlying disease process causing multiple sclerosis has continued to evolve since the initial approval of interferon-beta-1b in 1993. Current emphasis is on early treatment, including treatment after a single clinical attack (clinically isolated syndrome). The assessment of which disease modifying medication to use as initial therapy has continued to remain a combination of science and the art of medicine. Equally important are the assessment of treatment failure and the subsequent choice of medication change. This article will present scientific information, as well as information about clinical decision making, about these choices, with emphasis on the changing role of glatiramer acetate in this process.

Keywords: glatiramer acetate, early treatment, multiple sclerosis

Introduction
Most cases of multiple sclerosis (MS) are currently thought to be caused by an autoimmune process in which activated lymphocytes and other immune cells infiltrate the central nervous system (CNS) and cause inflammatory damage to the myelin sheath of axons. In recent years, it has become apparent that damage to the axons and neurons also occurs early in the disease process. In fact, damage to the axons and neuronal cell bodies may be a cause of greater permanent disability than myelin damage.

The underlying cause of this immune attack is unknown, but recent evidence implicates genetic, infectious and environmental factors in the development of this condition.

Many genes have been implicated in the disease process, with most being involved in either susceptibility to developing MS or determination of MS severity. No gene has been identified that actually causes MS. Many of the genes that have been identified are related, through uncertain biological mechanisms, to immune cell function or inflammatory molecule processes.

One or more infectious processes may serve as a trigger for the disease. Over the years many organisms have been suggested, but recent evidence has implicated the Epstein-Barr virus as the triggering organism in most, if not all, MS cases.

Finally, over many years, epidemiological studies have suggested that environmental factors may influence the development of MS. Recent data suggest that higher sunlight exposure and/or vitamin D supplementation in childhood may decrease the risk of MS, suggesting that this is the environmental factor implicated in the development of MS. Other recent data have suggested that vitamin D has effects on...
immune system function and abnormal genetic loci involved in vitamin D effects have been identified in MS patients.8

Current approved MS therapies

No approved treatments were available to control the disease process until 1993 when interferon-beta-1b (Betaseron® [Bayer], Betaferon® [Bayer], and recently, Extavia® [Novartis]) became the first approved drug shown to slow the disease process. This was followed within a few years by interferon-beta-1a (Avonex® [Biogen Idec], and, later, glatiramer acetate (Copaxone® [Teva], Rebif® [Merck Serono]).

The complete biochemical mechanism of action of these drugs is still unknown. The interferons are large molecules that interact with surface receptors on immunocompetent cells and stimulate certain internal genetic processes. The resultant proteins downregulate immune system function in multiple aspects, perhaps most importantly by reducing trafficking of activated lymphocytes across the blood–brain barrier (BBB) into the CNS. Other proposed effects of interferons on the immune system include inhibition of T-cell activation and proliferation, apoptosis of autoreactive T-cells, induction of autoreactive T-cells, induction of regulatory T-cells, inhibition of leukocyte migration across the BBB, cytokine modulation, and potential antiviral activity. Furthermore, there is some evidence of regenerative effects of endogenously produced interferon-beta within the CNS.9,10

Glatiramer acetate (GA), a synthetic amino acid co-polymer, is a small molecule that downregulates activated immune cells in some different fashion, but does not apparently affect migration across the BBB. Although the mechanism of action is not completely understood, it is felt that GA acts in the peripheral circulation by inducing GA-specific T cells. There is a subsequent induction of regulatory CD8+ and CD4+CD25+ T-cells in the periphery. These cells then cross the BBB and re-activate within the CNS, resulting in downregulation of myelin-specific immune cell activity. This in turn leads to increased production of anti-inflammatory cytokines and resultant neuroprotection. Furthermore, GA induces the production of neurotrophic factors, which might favor remyelination and axonal protection.11,12

In 2000 and 2001, mitoxantrone (Novantrone®; EMD Serono, OSI), a long-established chemotherapy drug, and interferon-beta-1a administered subcutaneously (Rebif) were approved to treat MS in the United States and other countries. Natalizumab binds to the surface of all white blood cells except neutrophils and reduces their ability to cross the BBB and therefore there is less damage to CNS myelin, axons and neurons. It was removed from the market by the drug company in 2005 due to the discovery of progressive multifocal leuko-encephalopathy in two MS patients and one patient undergoing investigational treatment for Crohn’s disease. It was re-introduced into the market in 2006 after review of available scientific data. Since the re-introduction, a number of progressive multifocal leuko-encephalopathy (PML) cases have occurred (currently about 0.67 per 1000 exposed patients worldwide, 1.1 per 1000 patients treated for 1 or more years, 1.59 for patients treated 2 or more years and 0.94 for patients treated 3 or more years). The survival rate for PML cases is about 76%. Surviving patients have minimal to severe deficits (BiogenIdec website data, April 6, 2010).

Thus, the six drugs currently approved to treat MS fall into four categories: interferon-beta, GA, chemotherapy and monoclonal antibody. As will be discussed later, the drugs with higher efficacy (mitoxantrone and natalizumab) often have more serious potential side effects.

Now that numerous drugs are available to treat MS and several more are expected to be available in the next few years, the choice of medication for treating MS patients has become increasingly complicated. This article will assist physicians in understanding the selection process, as well as strategies for evaluating the efficacy of the initial drug in individual patients and for changing therapies if necessary. The evolving role of GA in the treatment of MS will be emphasized in this article.

MS management issues

The treatment of MS has evolved over the years, as we have begun to increasingly understand the disease process more completely, as well as the effects of the available drugs in both groups of patients and individual patients. This has resulted in improved (although not perfect) selection of disease-modifying therapies (DMTs) for individual MS patients.

MS has been categorized into four clinical types: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and relapsing progressive MS (RPMS).

About 85% of patients initially present as RRMS. These patients have episodic clinical relapses (also termed exacerbations or attacks). Relapses are characterized by the development of new neurological symptoms and/or signs, usually progressing over hours to days, which subsequently
stabilize and then partially or completely resolve over weeks to months. Relapses may occur with greater or lesser frequency over time, usually thought to occur on average about once yearly. However, analysis of placebo-treated cases in recent studies has suggested that, at least earlier in the disease process, relapses may occur on average about once every 3 years.

When a patient presents with the initial clinical attack, this has been termed clinically isolated syndrome (CIS). This diagnosis generally requires an MRI scan of the brain and/or spinal cord, as well as blood and electrodagnostic testing to rule out MS mimics. In the past, the diagnosis of MS required two clinical attacks. CIS is now accepted as being equivalent to the diagnosis of RRMS for treatment decision purposes.

In recent years patients have been identified as having possible MS based on MRI scans of the brain or spinal cord alone, with no suggestion of clinical events. These MRI scans are generally performed for reasons other than to rule out MS (e.g., headache evaluation or cervical radiculopathy evaluation). When an MRI is consistent with MS, but the patient has no clinical symptoms related to MS, this is termed radiologically isolated syndrome (RIS).

Natural history studies have shown that up to about 85% of RRMS patients will develop SPMS over time if not treated. In this situation, patients demonstrate a slow progression of physical and/or cognitive disability not associated with clear-cut exacerbations. In some cases of SPMS, exacerbations of MS are superimposed on a background of slow deterioration. This form of the disease is called relapsing SPMS or SPMS with relapses.

About 10% to 15% of patients have PPMS. In this form of the disease, patients develop slowly progressive neurological deterioration over time, with no obvious clinical relapses. Most patients develop progressive lower extremity weakness initially, although other symptoms may occur in the early stages. Over time progression continues, but no exacerbations occur.

Unfortunately, the clinical disease process does not always correlate well with MRI findings and/or pathological findings. Some studies have shown several different pathological types of MS within the clinical RRMS type. Therefore, clinical MS type may not be scientifically useful to determine which MS medications work better in different pathological types. At this point, we do not have any scientific or clinical markers to predict which medication may work better in individual patients. Thus, we are left with the scientifically unsatisfactory process of choosing initial therapies and subsequent therapy changes on poorly defined clinical and MRI markers.

Choosing initial therapies

The diagnosis of MS requires clinical acumen to evaluate the patient history, examination findings and MRI/blood/urine/cerebral spinal fluid test results. No definite biological markers of the disease process exist. The detailed process of making the diagnosis of MS will not be described here, but at times the diagnosis cannot be reasonably certain. In these cases, the process of “watchful waiting” with scheduled examinations and periodic MRI scans of the brain with MS protocol (Consortium of MS Centers MRI Protocol for MS, 2009, mscare.org) are performed over time, often for several years.

However, once the diagnosis is made, treatment should be initiated as early as possible. Recent studies have documented the benefit of early treatment of CIS patients, beginning after the first clinical attack, rather than waiting until a second attack occurs. As a result, interferon beta-1a IM, interferon-beta-1b and GA have been approved for the treatment of CIS.

Unfortunately, some patients are reluctant to start therapy after they are diagnosed with CIS and/or MS. They do not want to be treated with expensive therapies requiring injections and having potential significant side effects when they have had a single attack of MS with full recovery. They feel normal again and are hopeful that they will have a mild case of MS and can delay treatment. In these cases it is helpful to discuss the plan of preventing disability, even when they feel normal. A useful tactic includes comparisons that patients understand. For example, they can usually understand such comparisons as treating hypertension to prevent strokes and heart attacks, treating seizures to prevent more seizures or wearing a seatbelt to prevent injury in the case of an accident. They need to be told that it is not a good idea to wait until they have permanent problems before starting preventative treatment.

Often it is difficult to convince a patient to start treatment at the same visit that the diagnosis of MS is made. They are often emotionally distraught by the diagnosis and cannot make reasonable choices about therapy at that time. They should be informed that treatments are available that can reduce disease activity and that they will need to be on therapy to reduce the likelihood of further attacks or progression in the future.

Patients can be referred to various websites or given the telephone numbers of MS organizations for more information.
and told to return in the near future for further discussions of therapy options. They should not simply be given packages of information and told to choose what they want to take. It is not reasonable for a patient newly diagnosed with MS to choose a therapy on their own. However, information is important in helping the patient and the physician to make the best choice. It is well known that medication will not help patients unless they take it. Therefore, it is important for patients to know what the options are in order to assure adherence to therapy once it is started.

When starting therapy, it is important to help them understand that side effects do not occur in every patient and that if they do occur, they often improve over time. Furthermore, especially with interferons, dose titration and prophylactic medication for flu-like syndrome is important to reduce side effects during initiation of therapy. Patients may be assisted in the start-up process by communication with other experienced MS patients, pharmaceutical company support programs and various MS charitable organization support programs. These should be offered to all patients at therapy initiation.

Patients mistakenly sometimes think that their initial choice of medication will be the only medication they can take indefinitely into the future. Patients should be made aware that each treatment has class and individual potential side effects and benefits, but if the initial therapy choice is not tolerable, other therapy can be selected. The initial choice is not necessarily a lifelong decision.

From the healthcare provider position, therapy choices are based on a balance of efficacy, tolerability and safety. Furthermore, as with many other fields of medicine, the prior experience and training of each provider will often influence the initial choice of medication. It is generally held that most providers will initiate therapy in most patients with an interferon or GA, as the risks of the more powerful drugs are too great to assume for initial therapy. However, some experienced physicians will choose a medication with greater efficacy that has a higher risk for patients who are considered to have a more aggressive form of MS.

The efficacy of GA and the various forms of interferons are felt to be similar by most physicians. Recent studies have shown nearly identical results on clinical and MRI parameters when comparing GA to interferon-beta-1a given subcutaneously (SQ) and also comparing GA to normal and double dose of interferon-beta-1b. There are some mild differences in MRI results between treatments, but this is variable. No direct comparisons of GA with interferon-beta-1a given intramuscularly (IM) have been undertaken. The phase III trials of each drug, while not directly comparable, suggest no overall benefit of either drug, but some smaller studies suggest superiority of GA.

There is some evidence that more frequent dosing of interferons is more effective than less frequent dosing, at least in the early stages of treatment, but neutralizing antibodies occur more often with the more frequently administered interferons and may affect efficacy after 18 to 24 months of therapy. A large retrospective study of nearly 4000 MS patients has shown no difference in interferons when switching from one to another. Other recent evidence has suggested that higher doses of interferons are generally not any more effective than the normally prescribed doses, but higher doses of GA may or may not provide additional benefit.

MRI results generally parallel the clinical markers of disease progression (especially if cognitive function is assessed). However, some recent evidence has shown less brain atrophy with GA, somewhat more atrophy with weekly interferon-beta-1a IM, and even more atrophy with more frequently administered interferon-beta-1a and interferon-beta-1b subcutaneously. A considerable amount of literature has demonstrated a potential beneficial effect of GA for tissue repair processes as well.

Another factor of some importance may be the potential of the treatment to be associated with pregnancy issues. GA is felt to have the least risk (package inserts for GA and all interferons); since many MS patients are young females of child-bearing age, this should be considered when choosing therapies.

In summary, the choice of initial therapy with a DMT involves an analysis of efficacy, safety and patient tolerability issues, as well as prescriber experience and training. There is no general consensus on initial therapy choice, except that it is usually GA or an interferon. Currently, GA is the most commonly prescribed DMT for MS both around the world and in the United States.

Switching therapies – medication intolerance

The initial choice of DMT is often well tolerated and continues to be effective over time in many MS patients. These patients will continue on their initial therapy indefinitely.

However, at times the initial therapy is not optimal for an individual patient and a change must be made. There are generally two reasons for switching therapy – intolerance of the current therapy or ineffectiveness of the current therapy. Unfortunately, just as with the choice of initial therapy, there
are no clear-cut definitions of therapy intolerance or loss of efficacy.

Therapy intolerance is often influenced by individual perceptions and individual tolerance to side effects. In fact, various adjustments in therapies and treatments for side effects, can improve tolerability of each of the medications. Many articles have been written about methodologies for improving patient tolerance and adherence to therapy. Details will not be discussed here, but a few points will be discussed.

Injections of any sort are often difficult to tolerate. At times, patients have great emotional difficulty with self-administration. Sometimes another person can be recruited to administer the injection. The patient sometimes experiences guilt about this need and counseling can be helpful. Also, additional nursing instructions and support may be necessary to continue self-injection. Of course, the necessity of taking medication to prevent neurological deterioration in the future is of utmost importance, but is often minimized by the patient if they are doing well neurologically. The “seat-belt analogy” noted earlier is often helpful in encouraging adherence.

Side effects of injections (see Table 1) are usually skin site injection reactions (generally with subcutaneous injections) and flu-like syndrome (interferons). Various changes in injection techniques, oral medications or cutaneous medications may be helpful in reducing or eliminating these reactions. Monitoring of hepatic and hematological function also needs to be performed with interferons. Depression is common in MS patients. Therefore, psychological function of MS patients needs to be routinely assessed (while on any medication). Of course, if interferons, there may be more frequent and/or more severe depression.

When a particular therapy is deemed intolerable, then an alternate therapy must be chosen.

Table 1 Side effect profile of glatiramer acetate and interferon-beta

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<thead>
<tr>
<th>Glatiramer acetate</th>
<th>Interferon-beta</th>
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<tr>
<td>Injection-site reactions</td>
<td>Injection-site reaction</td>
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<tr>
<td>erythema, itching, swelling, pain</td>
<td>erythema, itching, swelling, pain</td>
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<tr>
<td>Lipoatrophy and SQ nodules</td>
<td>Injection-site necrosis</td>
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<tr>
<td>Immediate post-injection reaction</td>
<td>Flu-like symptoms</td>
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<td>Hepatotoxicity</td>
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<td>Hematologic toxicity</td>
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<td>Increased spasticity</td>
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<td>Worsening of depression</td>
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<td>Neutralizing antibodies</td>
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For example, when a patient is taking an interferon, switching to another interferon may or may not be a reasonable strategy. Therefore, switching to fewer injections or to IM injections due to injection fatigue or injection site reactions may be reasonable, but switching when patients have hepatic, hematological or psychological adverse events is not. Most often when side effects occur on an interferon, GA is considered a reasonable switch.

Interferons can induce the production of neutralizing antibodies in some patients, most commonly with interferon-beta-1b, less with interferon-beta-1a SQ and least with interferon-beta-1a IM. Many physicians around the world monitor interferon neutralizing antibodies (Nabs) either routinely or when a patient has an exacerbation. Most, but not all, physicians feel that neutralizing antibodies reduce or eliminate the effectiveness of interferons. This is felt to be especially true in patients with higher titers (100 to 400 titer or higher). When neutralizing antibodies are present and persist with repeat testing (usually about 3 months after the initial positive test), it is reasonable to switch therapies. However, antibodies from one interferon cross-react with the other interferons, so an interferon NAb positive patient who is going to be switched will usually be switched to GA and not a different interferon. It is not unreasonable to routinely measure interferon NAbs at 18 months after the start of therapy, when they have appeared in most cases, and consider switching to another non-interferon DMT if NAbs are present in higher titers (100 or greater or up to 400 or greater based on expert opinion).

If a patient on GA is experiencing significant injection site reactions that cannot be managed with changes in injection technique or topical medications, then a switch to interferon is reasonable.

In occasional instances, if a patient needs to switch due to injection fatigue or inability to administer injections, natalizumab may be considered, even after only one drug “failure”. Although the risk of PML or other CNS infections with natalizumab is greater, the lower side effect profile, less frequent treatments and greater efficacy may outweigh the risk for individual patients.

Switching therapies – treatment failure

The concept of “treatment failure” based on clinical and/or MRI assessment is subject to individual opinions and expert consensus agreements. However, there is no consensus on assessment and measurement of treatment failure.
Clinical definitions of treatment failure usually involve frequency and/or severity of relapses or determination of overall disease progression. However, even the determination of what constitutes a relapse and how progression should be measured is open to individual interpretation.

Some patients feel that if their MS symptoms do not resolving or if they do not return to a fully functional status, then this means that the medication is not working. This misunderstanding requires education of the patients, often on more than one occasion, that the benefit of treatment is to prevent or reduce exacerbations in the future, not to repair all the damage that has already occurred.

As noted above, numerous publications have attempted to provide a definition of treatment failure and there is no consensus.\(^{30-32}\) The following assessment is a reasonable attempt to describe treatment failure. It has been a commonly held belief, based on assessment of placebo cases in early MS trials, that one exacerbation annually is average for an untreated patient. However, in a number of more recent placebo-controlled trials of drug efficacy, the relapse rate for untreated patients was approximately one every 3 years.\(^{33}\) Thus, the idea that a patient is “doing worse than placebo” is difficult to define. Furthermore, when looking at most long-term studies (5 to 12 years), it is apparent that many patients drop out for various reasons. However, when looking at the patients who remain on the study, the annualized relapse rate is about 0.2 to 0.25 (one relapse every 4 to 5 years). Therefore, a reasonable assumption may be made that more than one relapse in a 4- to 5-year period may be considered “treatment failure”. Again, there is no consensus on this definition of treatment failure.

The assessment of treatment failure due to disability progression is also fraught with difficulties. A commonly used measure, the Extended Disability Status Score (EDSS), is often used to define disease progression. A worsening by 0.5 to 1.0 points on the 10-point scale, sustained for at least 3 to 6 months, is considered a valid measure of disease progression. However, the scale is relatively insensitive to some functions, especially to fatigue, cognitive and emotional functions. Since these are common impairments in patients with MS, other scales have been utilized. However, no consensus has been reached regarding which scales to use routinely. A recent article\(^{34}\) has proposed a series of tests that are predominantly self-administered by patients before each physician visit to help assess overall function.

Finally, worsening of MRI scan lesion load has been suggested as a measure of disease progression and treatment failure. However, there is no consensus on what parameters to utilize. Suggestions for monitoring parameters have included T2 lesion load, T1 lesion load, gadolinium-enhancing lesion load, MR spectroscopy, total brain atrophy and gray matter atrophy, among others.

At this point, the determination of treatment failure remains more of an art than a science. In the opinion of the author, assessment of treatment failure is performed to determine whether or not to recommend a change in medications. Therefore, the author uses the following criteria to determine whether or not to discuss change in DMT with a patient:

1. One or more significant attacks in a 4- to 5-year period.
   The definition of a significant attack is variable. For example, mildly blurred vision in one eye lasting several days or mild tingling of the non-dominant hand lasting several days or a week would be considered a mild exacerbation. On the other hand, ataxia and hemiparesis requiring the new use of an ambulatory aid would be considered a significant attack, regardless of degree of recovery with or without steroids.
2. A new T2 CNS lesion on MRI, measuring 0.5 cm or greater, or a new gadolinium-enhancing or T1 lesion, even in a clinically silent area, is considered a sign of significant disease activity.
3. Progressive disability with persistent clinical alteration of motor, cognitive or sensory dysfunction lasting 6 months or longer, is considered a sign of disease progression. If one or more of these events are detected, then there should be consideration of a change in DMT.

### Switching therapies – which switch?

When the decision to switch is made, what DMT will be used? As noted above, it is reasonable to switch from an unsuccessful interferon to GA or vice versa. Since the interferons are somewhat similar in efficacy, a switch from one interferon to another due to lack of adequate efficacy does not seem reasonable. However, a switch from subcutaneous to intramuscular may be reasonable if injection site reactions or frequency/discomfort of injections are issues and the patient is doing well clinically otherwise.

Reasonable strategies are to switch from interferon to GA or vice versa; however, if a patient has “failed” both classes of therapy, then a switch to natalizumab or mitoxantrone is reasonable. Mitoxantrone is currently not used very frequently due to the risk of cardiac muscle damage, infection or leukemia, and other malignancies. Natalizumab is a reasonable choice and a recent publication suggests criteria for switching and following patients on this medication.\(^{35}\) This publication also suggests high-risk cases in which natalizumab may be
an appropriate DMT to use for initial therapy. Although natalizumab has a small risk of the development of PML, many MS patients and physicians consider the small risk reasonable when other therapies are failing.

Conclusions
MS is a recurrent and progressive auto-immune disease in which there is ongoing damage to the myelin, as well as the axons and nerve cell bodies, in the CNS. There is currently no known treatment to prevent or cure the disease, so all treatment is directed towards downregulation of the immune system within the CNS to slow the resultant tissue damage.

A number of studies have shown that starting treatment as soon as possible in the disease process reduces disability over time, so early diagnosis is imperative. Diagnosis after the first event is currently labeled CIS; this is considered the optimal time to initiate therapy. Currently in the United States, GA, interferon-beta-1a IM and interferon-beta-1b have received approval for treatment of CIS.

When choosing initial therapy in a newly diagnosed patient, it is most important that the patient actually adhere to the therapeutic regimen. Although patients should not simply be given information about all DMT drugs and told to choose their own therapy – they must participate in the decision-making process.

Generally patients are started on either GA or an interferon. Efficacy of the medications is generally considered similar, so decisions are often made based on tolerability, ease of use and safety.

GA is dosed daily, so it has the most injections monthly of all the current DMTs. On the other hand, it has fewer systemic side effects, no hepatic or hematological effects and low risk to fetal development. The last is of considerable importance in MS, since many MS patients are young females of childbearing age. Injection site reactions are fairly common, but generally are of minor significance. However, at times they are of sufficient severity to require a change in therapy. GA exhibits benefit in reducing relapse rates and disability progression. Studies of GA versus interferon-beta-1a SQ and interferon-beta-1b show essentially the same clinical efficacy and similar, but not identical, MRI efficacy. GA also shows experimental evidence of neuro-protection/neural repair and less brain atrophy than interferons. Therefore, it is an excellent choice for initial therapy.

Interferon-beta-1a IM is dosed least frequently of the four platform drugs (once weekly), but is given intramuscularly rather than subcutaneously. This may inhibit some patients who cannot self-inject intramuscular medication or obtain the assistance of another person. Side effects may be ameliorated with dose escalation and medication. Its efficacy is similar to that of the other therapies, although some studies have suggested a slower onset of action than other interferons. However, it is also considered an excellent choice for initial therapy due to its tolerability and efficacy.

Frequently administered interferons (interferon-beta-1a SQ and interferon-beta-1b SQ) are also reasonable choices for initial therapy, especially if patients desire subcutaneous injections that are given less frequently than Copaxone.

Uncommonly, initial therapy with natalizumab should be considered.

In summary, the most important factor in treating MS is to start early (CIS if possible) and prescribe a medication that the patient is likely to tolerate. If they don’t take the medication, it won’t work! Finally, if they are not tolerating or responding to a medication, early change to another therapy is recommended to prevent an increase in permanent MS-related disability.

Disclosure
The author has served as a speaker and advisor for Bayer, BiogenIdec, EMD Serono, and Teva Neurosciences.

References


