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Immunotherapy of multiple sclerosis—Current practice and future directions

Mark J. Tullman, MD; Fred D. Lublin, MD; Aaron E. Miller, MD

The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai Medical Center, 5 East 98th Street, Box 1138, New York, NY 10029

Abstract—Over the past decade, multiple sclerosis (MS) has become a treatable neurological disease. This paper reviews the therapies that have been studied to treat MS and discusses various treatment approaches on the horizon. Immunosuppressive and immunomodulatory therapies have been shown to alter the long-term course of MS. Therapies are currently available for relapsing-remitting, secondary progressive, and progressive relapsing disease. Although effective, these therapies have a modest impact on reduction in relapse rate and slowing of disease progression. Much work is needed to improve upon this modest effect and hopefully obtain a cure.

Key words: *disease-modifying agents, immunomodulatory, immunosuppressive, immunotherapy, multiple sclerosis, treatment.*

INTRODUCTION

In 1993, the first disease-modifying therapy was approved in the United States for treatment of multiple sclerosis (MS). Since then four additional agents have been approved, solidifying MS as a treatable neurological disease. Therapy is now available for relapsing-remitting (RR), secondary progressive (SP), and progressive relapsing (PR) MS (see **Figure**). There are no proven therapies for primary progressive MS (PPMS). As detailed in the following sections, the available therapies for MS are modest in their effect on reduction in relapse rate and slowing of progression of disease, but nevertheless, clearly effective. During the past decade, there have been many pilot and pivotal trials in MS, allowing for incremental improvement in clinical trial design and implementation. In addition to refining the clinical scales used to assess efficacy, employing many magnetic resonance imaging (MRI) metrics has allowed for more rapid assessment of treatment effect and a better understanding of the underlying immunopathologic process of MS.

Therapy for MS generally involves either disease-modifying agents (DMA) (i.e., those that alter the long-term course of MS), treatments of acute exacerbations, or symptomatic therapies. The latter are beyond the scope of this paper. The DMA segregate into immunosuppressive therapies, characterized by relatively nonspecific down-regulationof immune function and immunomodulatory therapy, where the effects on the immune system are more targeted and usually less toxic. Currently, the best-studied agents have been immunomodulatory.

TREATMENT OF ACUTE ATTACKS

Corticosteroids have anti-inflammatory and immunosuppressive effects. Although they likely do not alter the natural course of the disease, corticosteroids shorten the duration of an attack and hasten the time to recovery.

Address all correspondence and requests for reprints to Mark J. Tullman, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai Medical Center, 5 East 98th Street, Box 1138, New York, NY 10029; email: gmtullman@aol.com.

RR	Interferon ß-1a,* Interferon ß-1b, Glatiramer Acetate, Mitoxantrone†
SP	Mitoxantrone, Interferon ß-1b‡
PR	Mitoxantrone
PP	None§

* Both 30 µg IM once weekly and 44-µg SC thrice weekly have been shown to be effective in RRMS.
† Indicated in patients with worsening RRMS, despite treatment with interferon ß or glatiramer acetate.
‡ Two studies of interferon ß–1b in patients with SPMS have yielded conflicting results in disease progression.
§ Glatiramer acetate and mitoxantrone are currently being tested in PPMS.
RR = relapsing-remitting
SP = secondary progressive
PR = progressive relapsing
PP = primary progressive

Figure.
Successful therapeutic trials in MS by disease type.

They have been the mainstay of treatment for acute exacerbations in MS for more than 30 years (1–4). Whereas periodic pulse doses of intravenous (IV) methylprednisolone are not effective in preventing disability in patients with progressive MS, a recent phase II trial concluded that they do have an effect on disability in patients with RRMS (5,6).

Although no consensus exists on optimal dose, route, or length of therapy, currently, patients with acute attacks are often treated with high-dose IV methylprednisolone (500–1,000 mg/day) for 3 to 5 days, followed by an oral prednisone taper. While some neurologists treat acute relapses with oral prednisone, the results of the Optic Neuritis Treatment Trial question this practice. In this multicenter, blinded, randomized, placebo-controlled trial of acute unilateral optic neuritis, 457 patients were randomized to receive either oral placebo, oral prednisone (1 mg/kg) for 14 days or high-dose IV methylprednisolone for 3 days, followed by 11 days of an oral prednisone taper within 8 days of onset of visual symptoms (7). Although the vision in patients in the IV steroid- treated group improved more rapidly than those of the oral prednisone- or placebo-treated group, the visual acuity was similar in all three groups at 6 months. There was no difference in the rate of recovery between the placebo- and oral prednisone-treated groups. However, patients treated with oral prednisone were more likely to develop recurrent optic neuritis than were the patients in the other two groups. Patients treated with IV steroids had a statistically significant lower rate of the subsequent development of clinically definite MS over a 2-year period than did the patients in the other two groups (8). However, this effect was temporary and by the end of 3 years, no difference existed among the three groups (9).

Corticosteroids are well tolerated by most patients with MS (10). The side effects of short-term pulse doses include behavioral disturbances, aseptic necrosis of bone, promotion of osteoporosis, risk of infection, and possibly peptic ulceration. The long-term risks of pulse doses of corticosteroids are unknown. Thus, the risks and benefits of corticosteroids need to be considered individually. It is perhaps best to treat patients with mild symptoms and signs that are not bothersome (e.g., mild sensory symptoms) with a conservative approach.

The only other treatment shown to be effective for acute relapses in MS is plasma exchange (PE). In a small, double-blind, placebo-controlled crossover trial by Weinshenker et al., patients with severe attacks of inflammatory demyelinating disease (all patients had hemiplegia, paraplegia, or tetraplegia) who failed to improve after at least a 5-day course of high-dose parenteral corticosteroid therapy were randomized to receive either seven treatments of PE or sham exchanges over 14 days (11). More than 40 percent of patients treated with PE had considerable improvement of their neurological deficits compared with approximately 6 percent of those patients who received sham exchange. This improvement occurred early during treatment and was sustained during 6 months of follow-up. Those that responded were treated within an average of 40 days of onset of symptoms. One patient improved after treatment was begun 61 days after the onset of symptoms. The time from onset of symptoms to initiation of treatment was similar in those patients that responded to therapy and those that failed therapy.

A reasonable approach to the treatment of acute relapses of MS would seem to be a 3- to 7- day course of high-dose intravenous corticosteroid therapy. If a patient has significant residual disability after 7 days, a trial of PE may be warranted.

DISEASE-MODIFYING AGENTS

Immunomodulatory Therapy

There are four immunomodulatory agents, interferon ß-1a (Avonex and Rebif), interferon ß-1b (Betaseron), and glatiramer acetate (Copaxone), approved by the Food and Drug Administration (FDA) for the treatment of RRMS (12–18).

Interferon Beta

The mechanism of action of interferon ß (IFN ß) in MS is unknown. It has a wide range of effects on the immune cascade. Potential mechanisms include reduction in transport of T cells from the peripheral circulation into the central nervous system (CNS) through effects on adhesion molecules, chemokines, and matrix metalloproteinases; inhibition of type 1 T-helper cell activation and augmentation of suppressor T cell function; and alteration of cytokine production to favor an anti-inflammatory state (19).

Interferon ß-1b (IFN ß-1b) was the first treatment shown to have a favorable effect on the natural history of MS (12,13). It is produced in Escheria coli and differs from human IFN ß by two amino acids. Unlike human IFN ß, IFN ß-1b is not glycosylated. In 1993, the FDA approved IFN ß-1b for the treatment of RRMS. This approval was based on results of a multicenter, double-blind, randomized, placebo-controlled trial of 372 patients with a baseline Expanded Disability Status Scale (EDSS) of 0.0 to 5.5 who had at least two relapses in the previous 2 years (12,13,20). In this study, patients were randomized to receive either placebo, IFN ß-1b 1.6 million international units (MIU) (50 µg), or IFN ß-1b 8 MIU (250 µg) subcutaneously (SC) every other day for 2 years. The primary end points of the study were a reduction in exacerbation rate and the percentage of patients remaining exacerbation free. At the end of 2 years, the group of patients treated with IFN ß-1b 8 MIU had an exacerbation rate of 0.84 attacks a year compared with 1.27 attacks a year in the group treated with placebo, a statistically significant reduction of approximately 34 percent. At the end of 2 years, there was a significantly greater number of patients in the IFN-treated group who remained relapse free than in the placebo-treated group. However, when the study was extended, the difference was no longer significant after 3 years. Patients treated with the IFN ß-1b had a longer time to first and second relapse, fewer moderate to severe attacks, and required fewer hospitalizations. Confirmed progression of disability had no significant difference, as measured by an increase of one or more EDSS points that persisted for at least 3 months, between the IFN ß-1b and placebo-treated groups. Patients treated with IFN ß-1b had a significant reduction in MRI activity and burden of disease. The results of various outcome measures including exacerbation rate and MRI disease burden favored the higher dose treatment group and provided evidence for a possible dose effect.

Neutralizing antibodies (NAb) developed in approximately 38 percent of the patients treated with IFN ß-1b after 2 years (with most developing during the first year of treatment) and were associated with a decrease in clinical and MRI efficacy (12,20). After 18 months, the relapse rate of the group of patients treated with IFN ß-1b 8 MIU who were NAb positive was similar to the group of patients receiving placebo (21). However, over time, NAb disappeared in the majority of patients, and Rice et al. have recently suggested that the measurement of NAb may have little clinical use and the treatment decisions should be made exclusively on clinical grounds (22).

In the Independent Comparison of Interferon (INCOMIN) trial, IFN ß-1b 8 MIU given SC every other day and IFN ß-1a (Avonex) 6 MIU once weekly were compared in patients with RRMS (23). After 6 months of treatment with IFN, the two had similar clinical effects. However, after 1 year, IFN ß-1b was superior in various unblinded clinical outcomes, including relapse rate and sustained EDSS progression. Similarly, MRI results (evaluated in a single-blind manner) favored the IFN ß-1b-treated group. The recently presented 2-year results showed a similar outcome.

IFN ß-1b has also been shown effective in SPMS (24). In a multicenter, double-blind, randomized, placebo-controlled European trial, 718 patients with SPMS (EDSS 3.0 to 6.5) were randomized to receive either IFN ß-1b 8 MIU or placebo SC every other day for up to 3 years. The primary outcome was time to confirmed progression of disability measured by a sustained increase of at least 1.0 point on the EDSS (0.5 point if the EDSS was ≥ 6.0). The mean follow-up for both groups was approximately 900 days. In this study, the group treated with IFN ß-1b had an approximate 22-percent reduction in the time to progression with an average delay of 9 to 12 months. During the study period, nearly one-third fewer patients in the IFN ß-1b-treated group became wheelchair-bound compared with the placebo-treated group. In addition, patients in the IFN ß-1b-treated group had a significant reduction in

relapse rate, had longer time to first relapse, required fewer hospitalizations, and had less steroid use. Positive results were also seen for MRI analysis (25). A second study of IFN ß-1b in SPMS was performed in North America and was recently reported but not yet published (26). In this study, SPMS patients were treated with either placebo, IFN ß-1b 8 MIU SC every other day, or IFN ß-1b 5 MIU/m² (this group received an average dose of 9.6 MIU) subcutaneously every other day. As opposed to the European study, this study showed no effect on the primary outcome assessment of time to confirmed progression of disability. Similar to the European study, other outcome measures, such as reduction in relapse rate and MRI activity and lesion load, favored the treatment group.

IFN ß-1b is currently approved by the FDA in ambulatory patients with RRMS to reduce the frequency of relapses. The usual dose is 8 MIU (250 µg) SC every other day.

IFN ß-1a (Avonex) is produced in mammalian cell culture and is structurally identical to human IFN ß. The pivotal trial of Avonex was a multicenter, double-blind, randomized, placebo-controlled trial of 311 patients who had RRMS with a baseline EDSS of 1.0 to 3.5 and had at least two exacerbations in the previous 3 years (14). These patients were randomized to receive Avonex 6 MIU (30 µg) or placebo via intramuscular (IM) injection once weekly. As opposed to the trials of the other interferons and glatiramer acetate, the primary outcome measure was time to sustained progression of at least 1.0 point on the EDSS. After 2 years, there was a significant treatment effect. Approximately 35 percent of patients in the placebo-treated group had sustained progression of disability compared with approximately 22 percent of patients in the Avonex-treated group. Several clinical and MRI measures served as secondary outcome events. For patients who received Avonex for 2 years, the annual exacerbation rate was reduced by 32 percent from 0.9 to 0.61. However, intent to treat analysis only demonstrated an 18-percent reduction in relapse rate. There was a significant reduction in the mean number and volume of gadolinium-enhancing lesions in the Avonex-treated group. After 1 year, the MRI total volume of T2-weighted lesions was significantly reduced in the IFN-treated group. However, by the end of 2 years, no significant difference existed between the two groups. Neutralizing antibodies developed in 22 percent of patients after 2 years.

There is ongoing debate as to when to initiate prophylactic therapy in patients with MS. The current practice guidelines from the National MS Society state that initiation of therapy with an immunomodulatory agent should begin as soon as possible following a definite diagnosis of MS and determination of a relapsing course (27). In the recent CHAMPS study, a multicenter, double-blind, randomized, placebo-controlled trial involving 383 patients, it was shown that initiating treatment with Avonex at the time of a first clinical demyelinating event (optic neuritis, incomplete transverse myelitis, brain stem, or cerebellar syndrome) in patients with MRI evidence of prior subclinical demyelination (defined as two or more clinically silent lesions greater than 3 mm in diameter, one of which had to be periventricular or ovoid) is beneficial in reducing the probability of developing clinically definite MS (28). Over 3 years, the rate of developing clinically definite MS was 44 percent lower in the group of patients treated with Avonex than the group of patients treated with placebo. However, at the end of 3 years, 50 percent of the placebo-treated patients did not have a second acute demyelinating event. Thus, although the course of MS is unpredictable, treatment may be unnecessary in a significant proportion of patients after a single clinical demyelinating event (i.e., before a diagnosis of clinically definite MS).

Currently, the FDA has approved the Avonex form of IFN ß-1a for relapsing forms of MS to slow the accumulation of disability and to reduce the rate of relapses. The approved dose is 6 MIU (30 µg) IM weekly.

IFN ß-1a (Rebif) is produced in Chinese hamster ovary cells and is structurally identical to human IFN ß and Avonex. It was tested in Europe and Canada in a multicenter, double-blind, randomized, placebo-controlled study involving 560 patients with RRMS (EDSS 0.0 to 5.0) with at least two relapses in the previous 2 years (15,16). Patients were randomized to receive placebo, Rebif 6 MIU (22 µg), or Rebif 12 MIU (44 µg) SC three times a week for 2 years. The primary outcome measure of the number of relapses over 2 years was obtained with a reduction of 33 percent in the Rebif 12 MIU-treated group and a 27 percent reduction in the Rebif 6 MIU-treated group. Patients in both treatment groups performed significantly better than the placebo group with respect to a number of moderate to severe relapses, time to first relapse, percentage of patients relapse free, percentage of patients requiring steroid use, and time to sustained progression of disability. MRI

analysis revealed a significant decrease in disease burden and fewer gadolinium-enhancing lesions in both treatment groups compared to the placebo group. Similar to what was seen in the IFN ß-1b RRMS trial, a dosing effect was suggested with the lower-dose treatment group having intermediate results in clinical and MRI outcomes. After 2 years, the study was extended an additional 2 years with the placebo group crossed over and randomized to receive either IFN ß-1a 6 MIU or 12 MIU three times a week (29). The treatment effect on clinical and MRI measures was maintained during the study for both doses of Rebif, with the higher dose group receiving the most benefit. Results were superior for patients treated with Rebif for all 4 years than for patients in the crossover groups, suggesting that early treatment may be more beneficial. After 2 years, NAb developed in roughly 24 percent of the low-dose treatment group and 12.5 percent of the high-dose treatment group, and their presence did not affect the mean number of relapses (15). After 4 years, the proportion of patients that developed persistent NAb was similar, but their presence was associated with reduced clinical and MRI efficacy (29).

In the Evidence for Interferon Dose-Response: European-North American Comparative Efficacy (EVIDENCE) trial, the two forms of IFN ß-1a (Avonex 6 MIU IM weekly versus Rebif 12 MIU three times per week) were compared in patients with RRMS in a multicenter, evaluator-blinded study (30). The 24-week data (the only results published thus far) demonstrated a superior effect of Rebif on relapse rate, time to first exacerbation, proportion of patients relapse-free, and steroid use. MRI outcomes also favored the Rebif-treated group.

Rebif was also tested in SPMS in a multicenter, double-blind, randomized, placebo-controlled trial of 618 patients (31,32). Although MRI outcomes and relapse rate in the Rebif-treated groups had positive results, the primary outcome measure of time to confirmed progression of disability was not significantly prolonged.

Based on the data from the EVIDENCE trial, the FDA approved Rebif for use in RRMS in March 2002. The usual dose is 12 MIU (44 µg) three times per week.

The main side effects of the interferons are flu-like symptoms, injection site reactions, and laboratory abnormalities. The flu-like symptoms (e.g., fever, chills, and myalgia) usually occur several hours after injection and often resolve within 24 hours. They can be especially problematic in the first few weeks after the introduction of treatment and may lead to noncompliance and even discontinuation of the drug. However, they generally resolve within a few months of initiation of therapy, and by the end of 1 year, such symptoms are reduced markedly (20). The flu-like symptoms can often be managed with nonsteroidal anti-inflammatory medications or acetaminophen and/or a gradual increasing dose escalation. Interferon is frequently given at night to limit side effects during wakefulness. All the interferons have been associated with injection site reactions that may be as mild as local redness to rarely as severe as skin necrosis requiring surgical debridement. Skin necrosis is much less common with Rebif than Betaseron (12,15). There have been no reports of skin necrosis associated with the use of Avonex. Injection site reactions can be reduced by proper injection preparation and technique.

A mild increase in liver enzymes, thrombocytopenia, anemia, or leukopenia may be seen shortly after initiation of therapy with the various interferons and usually returns to near baseline by 4 months. However, laboratory abnormalities may develop at any time during therapy. A complete blood count and liver function tests should be obtained before starting therapy and monitored during the course of treatment (4 to 6 weeks after initiating treatment, at 3 months, and every 3 to 6 months thereafter). Patients taking other medications that can cause hepatotoxicity or myelosuppression require more careful laboratory monitoring.

The interferons may possibly cause or worsen depressive symptoms (12,20,29). MS patients have a high prevalence of depression and suicidal ideation (33–35). Patients on interferon should be evaluated routinely for symptoms of depression. IFN ß-1b causes menstrual irregularities in some women. No drugs are known to interact with the interferons. They are contraindicated in patients with hypersensitivity to the drug. Women who are pregnant, trying to become pregnant, or are lactating should not use interferons.

Glatiramer Acetate (Copaxone)

Glatiramer Acetate (GA) is a synthetic polypeptide composed of four amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. Its mechanism of action is unknown but may be related to its capability to enhance suppressor T cells or to act as an altered peptide ligand (36).

In a pivotal multicenter, double-blind, randomized, placebo-controlled trial, 251 patients with RRMS with an EDSS of 0.0 to 5.0 and who had at least two relapses in

the previous 2 years were randomized to receive either placebo or GA 20 mg SC daily for 2 years (17). The primary outcome measure of a reduction in relapse rate was achieved with a 29-percent reduction from 0.84 in the placebo-treated group to 0.59 in the GA-treated group. The sustained progression of disability had no significant difference (as defined by an increase of at least 1.0 point on the EDSS maintained for more than 90 days) between the two groups. A subsequent MRI study demonstrated that when compared with placebo, GA significantly reduced the number of new T2-weighted and gadolinium-enhancing lesions (18). However, this effect occurred more slowly and less intensively than seen with IFN ß, suggesting that GA exerts its beneficial effect by a different mechanism of action than IFN ß. A large trial of GA in PPMS is currently underway (37).

GA is generally well tolerated, and the most common side effects noted during the trial were injection site reactions and a systemic reaction. The injection site reaction consisted of mild redness and induration at the injection site. There have been no reports of skin necrosis associated with its use. An unpredictable, sporadic transient systemic reaction occurred in 15 percent of patients receiving GA in the trial. This reaction consisted of a combination of chest tightness, flushing, shortness of breath, palpitations, and anxiety. It occurred within minutes of injection and was self-limited, lasting for seconds to minutes and resolving spontaneously without sequelae. In most patients, it occurred only once. GA does not cause anemia, leukopenia, or liver enzyme abnormalities, and routine laboratory studies are not necessary. GA does not cause depressive symptoms. No drugs are known to interact with GA. It is contraindicated in patients with hypersensitivity to the drug or to mannitol. Women who are pregnant or who are lactating should not use GA. Neutralizing antibodies do not develop against GA. GA is currently FDA approved in patients with RRMS for the reduction of relapses. The standard dose is 20 mg SC every day.

Although they certainly are not a cure with a relapse reduction of approximately one-third, the DMA that have become available in the past decade have provided MS patients with hope for a brighter future. According to the National MS Society Disease Management Consensus Statement, therapy should be continued indefinitely, unless a benefit is clearly lacking, side effects are intolerable, new data that reveal other reasons for cessation, or better therapy becomes available (27).

IMMUNOSUPPRESSIVE THERAPIES

Mitoxantrone (Novantrone)

Mitoxantrone is a synthetic anthracendione that intercalates into deoxyribonucleic acid (DNA), producing cross- links and strand breaks. It also interferes with ribonucleic acid (RNA) synthesis. It is indicated to treat pain related to advanced hormone refractory prostate cancer and as initial therapy of acute nonlymphocytic leukemia. Several small randomized, controlled trials suggested that mitoxantrone may have a beneficial effect on clinical and MRI measures in patients with MS (38–40). These results were confirmed in a larger multicenter, observer-blind, randomized, placebo-controlled trial in patients with severe RRMS, SPMS, or PRMS (41,42). In this trial, 194 patients were randomized to receive placebo, mitoxantrone 5 mg/m², or mitoxantrone 12 mg/m² intravenously every 3 months for 2 years. A cohort of 110 patients received annual MRI scans. Mitoxantrone significantly reduced the mean change in EDSS; EDSS decreased by 0.12 and 0.23 in mitoxantrone 12 mg/m² and 5 mg/m² treated groups, respectively, and increased by 0.23 in patients in the placebo group. There were also significant differences favoring mitoxantrone on various clinical measures, including the number of relapses, ambulatory impairment, and proportion of patients with confirmed EDSS progression. Patients in the higher dose mitoxantrone group had superior results in most outcomes. On MRI analysis, mitoxantrone significantly reduced the number of gadolinium-enhancing lesions and the average number of new T2-weighted lesions.

The major toxicities of mitoxantrone are bone-marrow suppression and dose-related cardiotoxicity (reduced left ventricular ejection fraction (LVEF) and irreversible congestive heart failure (CHF)). Treatment with mitoxantrone is limited to a cumulative lifetime dose of 140 mg/m² (2 to 3 years in most people). Evaluation of LVEF is recommended before therapy is initiated. According to the mitoxantrone product insert, MS patients with LVEF that is less than 50 percent ordinarily should not receive mitoxantrone (43). Further assessment of LVEF is recommended in patients who develop symptoms of CHF and before all doses in patients who have received a cumulative dose greater than 100 mg/m². Other side effects include alopecia, nausea, menstrual irregularities, and elevated liver enzymes. A complete blood count and liver function tests should be monitored before each dose. Mitoxantrone is contraindicated in patients with

hypersensitivity to the drug. It should not be used during pregnancy or lactation.

In 2000, the FDA approved mitoxantrone for the treatment of SPMS, PRMS, and worsening RRMS. The recommended dose is 12 mg/m² intravenously every 3 months. This agent is currently being tested in PPMS (44).

Azathioprine (Imuran)

Azathioprine is an imidazolyl derivative of 6-mercaptopurine that impairs DNA and RNA synthesis. It is used in a variety of autoimmune disorders, including myasthenia gravis. In a meta-analysis of seven randomized, blind, controlled trials with 793 patients with all forms of MS, azathioprine was shown to significantly reduce relapse rate at 1, 2, and 3 years (45). At 1 year, the change in EDSS was similar in the treated and control groups. After 2 years, there was a trend toward slowing disease progression favoring the azathioprine-treated group. A small retrospective study analyzed MRI lesion load in patients with RRMS (46). This study compared two serial MRI scans (mean interval between scans was 2.5 years) of patients treated with azathioprine and steroids after acute relapses with the scans of patients treated with steroids alone. A significant reduction in MRI lesion load was seen in the group treated with azathioprine and steroids.

Toxicities of azathioprine include bone marrow suppression, nausea, vomiting, and liver enzyme elevations. An increased risk of cancer may possibly exist with long-term use of azathioprine (47). It should not be used during pregnancy.

Overall, azathioprine has been shown to have a modest effect on relapses but no convincing effect on progressive disease. Despite this, azathioprine is probably the most common cytostatic agent used in progressive MS, based primarily on desperation and anecdotal reports.

Cladribine (Leustatin)

Cladribine is an adenosine deaminase-resistant purine-nucleoside analogue. It is an immunosuppressant that preferentially targets lymphocytes. It is used in the treatment of hairy cell leukemia.

Several small, randomized, double-blind, placebo-controlled studies suggested that cladribine may have a favorable effect on clinical and MRI outcomes in patients with RRMS and progressive MS (48–50). Subsequently, cladribine was studied in a larger, randomized, double-blind, placebo-controlled trial in patients with progressive MS (51). This poorly designed study did not demonstrate any clinical benefit after 1 year but did show a marked reduction in gadolinium-enhancing lesions in the cladribine-treated group. Side effects of cladribine include long-term bone-marrow suppression, fever, fatigue, nausea, and diarrhea. It should not be used during pregnancy.

Cyclophosphamide (Cytoxan)

Cyclophosphamide is an alkylating agent with cytotoxic and anti-inflammatory effects that is used to treat neoplastic and autoimmune disorders. Several studies of cyclophosphamide in patients with MS have yielded conflicting results (52–54). Comparison between trials is always hazardous, and various induction protocols have been used, some with the addition of steroids and/or plasmapheresis. The Canadian Cooperative Study provides the strongest evidence for its lack of efficacy (55). In this multicenter, single-blind, placebo-controlled trial, 168 patients with progressive MS were randomized to receive intravenous cyclophosphamide and oral prednisone; oral cyclophosphamide, oral prednisone, and weekly PE; or placebo medications and sham exchange. Patients were followed for an average of 2.5 years. No significant differences existed between the three groups in the primary outcome of progression of disease. Nevertheless, there are many anecdotes of success leading to use of this agent in desperate cases. Toxicities of cyclophosphamide include alopecia, nausea, vomiting, hemorrhagic cystitis, sterility, and malignancy. The drug is teratogenic and should not be used during pregnancy.

Cyclosporine (Sandimmune)

Cyclosporine is a cyclic polypeptide with potent immunosuppressive properties. It appears to suppress T-helper cells. Its main use is in transplant recipients. In a large multicenter, double-blind, placebo-controlled trial, 557 patients with progressive MS were randomized to receive either cyclosporine or placebo for 2 years (56). While there was a significant delay in the time to becoming wheelchair-bound and a significant reduction in mean change in EDSS in the cyclosporine-treated group, no significant difference existed in the time to sustained progression of disability or time to dependency in activities of daily living. The cyclosporine-treated group had considerable toxicity (mainly nephrotoxicity and hypertension). In

summary, cyclo-sporine has a modest therapeutic effect and significant toxicity.

In addition to nephrotoxicity and hypertension, other toxicities of cyclophosphamide include tremor, seizures, headache, paresthesias, hirsutism, gingival hyperplasia, and elevated liver enzymes. Cyclosporine use is also associated with an increased incidence of future malignancies. It should not be used during pregnancy.

Methotrexate

Methotrexate impairs DNA and RNA synthesis by inhibiting dihydrofolate reductase. It has potent immunosuppressive and anti-inflammatory activity and is used to treat malignancies, psoriasis, and a variety of autoimmune disorders. Methotrexate was studied in patients with progressive MS in a randomized, double-blind, placebo-controlled trial (57). In this trial, 60 patients with progressive MS with EDSS scores of 3.0 to 6.5 were randomized to receive either 7.5 mg of methotrexate or placebo orally every week for 2 years. In this small study, the rate of sustained progression of disability had a significant decrease, as determined by a composite of four outcome measures, from roughly 83 percent in the placebo-treated group to 52 percent in the methotrexate-treated group. However, when the components of the composite were analyzed individually, there was a significant effect on upper extremity function, but not on ambulation or EDSS. Of the 60 patients in this study, 56 had at least one annual MRI scan with gadolinium and a cohort of 36 patients received an MRI scan with gadolinium every 6 weeks for 6 months (58). In the cohort with scans every 6 weeks, a positive effect was seen in the methotrexate-treated group, with a significant reduction in T2-weighted total lesion area compared with the placebo-treated group. However, in the 56 patients with at least one annual scan, no significant difference existed between the two groups in change from baseline in T2-weighted total lesion area at 1 and 2 years. Enhancing lesions on the 6-week and annual scans were uncommon.

In this study, methotrexate was well tolerated, with adverse reactions similar to those of patients in the placebo group. However, major toxicities are associated with the long-term low doses of methotrexate, including interstitial pulmonary fibrosis, hepatotoxicity (liver enzyme abnormalities, hepatic fibrosis and cirrhosis), and bone-marrow suppression. Methotrexate can cause spontaneous abortions and teratogenesis and should not be used during pregnancy.

Autologous Stem-Cell Transplantation

Several reports and small studies have been done on the use of autologous stem-cell transplantation in patients with MS with a progressive course despite immunomodulatory and other immunosuppressive therapy (59–63). Small studies have reported clinical and radiographic successes, but a controlled study has not been done to date. In addition to the significant morbidity associated with the procedure, seven mortalities (five transplant-related complications and two secondary to progressive disease) occurred of the 102 patients registered with the European Group for Blood and Marrow Transplantation registry (63). Further testing of various protocols is underway or planned, hopefully in a controlled manner.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIG) has immunoregulatory and anti-inflammatory effects. It is used in a variety of autoimmune disorders, including myasthenia gravis and Guillain Barré syndrome.

The Austrian Immunoglobulin in MS Study was the first randomized, double-blind, placebo-controlled trial of IVIG in MS (64). In this study, 148 patients with RRMS and with an EDSS score of 1.0 to 6.0 were randomized to receive either IVIG 0.15 to 0.2 g/kg or placebo every month for 2 years. IVIG significantly reduced the relapse rate by 49 percent from 0.83 to 0.42. No data were offered on confirmed EDSS change. A second study also showed that IVIG reduced the relapse rate in patients with RRMS, but it had no effect on EDSS or MRI lesion score (65). However, one of the original investigators of this trial has questioned the blinding of this study (66). A small randomized, double-blind crossover trial found that IVIG at 2 g/kg/month reduced the number of new and total MRI gadolinium-enhancing lesions. However, there was no treatment effect on T2-weighted total lesion load, relapse rate, or disease progression (67). A large multicenter European and Canadian trial of IVIG at 1 g/kg/month in SPMS with clinical and MRI outcomes was recently completed (68); unpublished data have been presented and were apparently entirely negative. These results diminish the prospects and potential of IVIG in the long-term treatment of MS.

In women with MS, the relapse rate is reduced during pregnancy, increased during the first 3 months postpartum, and returns to the prepregnancy rate by 4 months

postpartum (69). A recently published study suggests that IVIG may reduce the risk of relapse during the first 3 months postpartum (70). In this study, 31 women were treated with IVIG 60 g within 3 days after delivery. Patients with active MS before pregnancy were also treated with an additional 10 g IVIG each month after delivery. All the women breast-fed for at least 4 weeks. When compared to the data from the prospective Pregnancy in Multiple Sclerosis (PRIMS) study, patients in this study had a similar reduction in relapse rate during pregnancy (69). Although the relapse rate increased after delivery in the women treated with IVIG, it was one-third lower than expected from the PRIMS data. In addition, 94 percent (17/18) of the women treated with monthly IVIG remained relapse free at 3 months postpartum. In the PRIMS study, there were 68 relapses in 222 women during the first 3 months postpartum.

Minor side effects of IVIG include low-grade fevers, chills, myalgias, headache, nausea, vomiting, and rash. Major toxicities include acute renal failure, aseptic meningitis, congestive heart failure, hypotension, deep venous thrombosis, and the possibility of anaphylaxis in patients with IgA deficiency.

FUTURE DIRECTIONS

The treatment of MS has been revolutionized over the past decade. Although MS is thought to be an inflammatory autoimmune disease, its cause remains unknown. Much work needs to be done to improve upon the current therapies and perhaps ultimately obtain a cure. Hopefully, in the near future, the optimal dose and route of administration of corticosteroids and the immunomodulators will be determined. Combination therapies with interferons, glatiramer acetate, mitoxantrone, and possibly others need to be studied. Lublin et al. recently reported that the combination of IFN ß-1a (Avonex) and glatiramer acetate is safe (71). A trial to determine whether the two have an additive or synergistic effect is eagerly awaited.

It has been speculated that the process of demyelination in MS begins when genetic and environmental factors trigger autoreactive T cells from the peripheral circulation to cross the blood brain barrier (BBB) and enter the CNS (72). Adhesion molecules, chemokines, and matrix metalloproteinases further enhance their entry. The release of proinflammatory cytokines initiates an immune cascade that ultimately leads to injury of myelin, oligodendrocytes, and axons. Many potential immunomodulatory targets exist for therapeutic intervention, but results thus far have been disappointing and, in some cases, have suggested worsening of the disease. Tumor necrosis factor (TNF) alpha (a proinflammatory cytokine) worsens experimental allergic encephalomyelitis (EAE), and anti-TNF antibody prevents animals from developing EAE (73–75). Two MS patients treated with a monoclonal anti-TNF antibody had an increase in MRI activity, cerebrospinal leukocyte counts, and IgG index (76). A large phase II study found that lenercept, a recombinant TNF receptor fusion protein, actually increased the exacerbation rate (77). Phosphodiesterase inhibitors (PDEIs) suppress TNF alpha in mice (78). The results of a recently published pilot study suggest that the combination of three PDEIs is safe and reduces the relapse rate in patients with MS (79). In a phase I trial, transforming growth-factor-ß 2, a pleiotropic cytokine, had no clinical or MRI benefit in patients with SPMS (80). Forty-five percent (5/11) of the patients in this study developed reversible nephrotoxicity. Other potential therapies include costimulatory and adhesion molecule blockers, matrix metalloproteinase inhibitors, major histocompatibility complex inhibitors, immunomodulatory therapy with altered peptide ligands, and T cell vaccination (81). Embryonic stem cell or Schwann cell transplantation and neuroprotection may be a means of restoring myelination and limiting axonal damage that could lead to functional recovery.

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