



# Current and Investigational Therapies Used to Alter the Course of Disease in Multiple Sclerosis

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**ABSTRACT:** Extensive research is under way to develop pharmacotherapeutic agents that will prevent the exacerbations and the progression of neurologic disability associated with multiple sclerosis (MS). The most intensive research strategy has involved agents intended to limit demyelination by reducing inflammation and modifying the immune response. In this category are interferon beta-1b, the first compound approved for use outside of clinical trials; interferon beta-1a; and copolymer 1. Experimental agents include other interferons, methotrexate, linomide, monoclonal antibodies, T-cell receptor peptides, and 2-chlorodeoxyadenosine. Although they have been used effectively to treat exacerbations of MS, corticosteroids and corticotropin are now under evaluation as disease-modifying agents. A second strategy, enhancing remyelination by limiting demyelination and oligodendrocyte injury, is represented by protein growth factors. A third therapeutic approach, improving conduction in demyelinated fibers, is represented by the potassium channel blockers 4-aminopyridine and 3,4-diaminopyridine.

MULTIPLE SCLEROSIS (MS) is a demyelinating disease of the central nervous system that is marked by focal or multifocal destruction of myelin sheaths accompanied by inflammation. Limited axonal destruction may also occur. Clinically, MS is characterized by recurrent attacks of neurologic dysfunction.

From a pathophysiologic standpoint, MS can be identified by the presence of diffuse, discrete demyelinated areas, called plaques. As the disease progresses, plaques increasingly arise in the paraventricular areas of the cerebrum, in the subpial area, and within the brain stem and spinal cord. A local breakdown of the blood-brain barrier occurs in areas of active lesions.<sup>1</sup>

Although the etiology of MS remains unknown, epidemiologic studies suggest that both environmental and genetic factors play a role.<sup>2</sup> MS is now widely viewed as an autoimmune disease that develops early in life in the

genetically susceptible person, perhaps after a viral infection initiates a T-cell-mediated immune response.<sup>3</sup>

Multiple sclerosis is usually classified according to one of four recently standardized clinical courses: relapsing-remitting, primary-progressive, secondary-progressive, or progressive-relapsing.<sup>4</sup> In the relapsing-remitting form, which accounts for two thirds of cases at the onset of the disease, attacks occur randomly over many years.<sup>5</sup> The extent of recovery among patients and from attack to attack is variable, but permanent deficits can accrue with each exacerbation, especially later in the course of the disease.<sup>5,7</sup> This neurologic deterioration, which may still be punctuated by intermittent acute attacks, is classified as secondary-progressive, as opposed to primary-progressive, and progressive-relapsing. These forms are progressive from the onset.<sup>4</sup>

## EVALUATION OF DISEASE BURDEN

Depending on the location of the lesions, signs and symptoms of MS may include vision disturbances, nystagmus, dysarthria, diminished perception of vibration and position sense, ataxia and intention tremor, weakness or paralysis of one or more limbs, spasticity,

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and bladder disorders. Neurologic abnormalities that are highly suggestive of MS are optic neuritis, internuclear ophthalmoplegia, and Lhermitte's sign, which is often described as an electrical sensation that passes down the back and into the legs when the neck is flexed.<sup>8</sup>

Disability attributable to MS is usually measured by the Expanded Disability Status Scale (EDSS) developed by Kurtzke.<sup>9</sup> This system uses findings from a standard neurologic examination to establish a functional status score. Functional systems scores and gait then guide the evaluator in assessing clinical impairment with the EDSS, which defines disability in half-point increments ranging from 0 (normal neurologic findings) to 10 (death due to MS).

Magnetic resonance imaging (MRI) provides the most accurate assessment of disease burden, identifying multifocal cerebral white matter lesions in more than 90% of people with MS.<sup>2</sup> Even when there are no clinical signs, serial MRI studies of patients with relapsing-remitting MS can identify developing lesions.<sup>2</sup> In fact, it is now well established that new lesions as identified by MRI occur 5 to 10 times more often than clinical changes.<sup>10</sup> Recent refinements in MRI, such as gadolinium enhancement, magnetization transfer, and magnetic resonance spectroscopy, have improved the sensitivity of detecting MS-associated lesions.<sup>11</sup>

#### TREATMENT OF MULTIPLE SCLEROSIS

Current therapy for MS includes relief of symptoms, amelioration of exacerbations, and reduction in the number of exacerbations and subsequent progression of neurologic disability. Symptomatic treatment addresses both the physical and psychologic needs of the patient. It includes pharmacotherapy, diet, energy conservation, physical therapy, patient and family counseling, support groups, mechanical devices, and surgery.<sup>12,13</sup> Exacerbations are usually treated with corticosteroids or corticotropin (ACTH), and administration of high doses of intravenous methylprednisolone (IVMP) has become particularly widely used.<sup>13</sup>

The third area of MS therapy, preventing exacerbations and progression of neurologic disability associated with the disease, has stimulated various approaches. These can be grouped into three major categories: limiting demyelination by reducing inflammation and regulating the immune response, enhancing

remyelination by limiting demyelination and oligodendrocyte injury, and improving conduction in demyelinated fibers.<sup>3</sup> The remainder of this review discusses each of these therapeutic strategies and the specific treatments that have been developed, or are in development, in response to each approach.

#### EFFORTS TO LIMIT DEMYELINATION

Most pharmacologic treatments aimed at reducing or preventing exacerbations of MS and associated neurologic disability fall into the category of limiting demyelination by reducing inflammation and suppressing the immune response.<sup>3</sup>

##### *Interferon beta*

The first agent shown to alter the natural course of MS by reducing the frequency of clinical exacerbations is interferon beta-1b (IFN $\beta$ -1b [Betaseron]), a recombinant interferon-beta produced in *Escherichia coli*. IFN $\beta$ -1b differs from natural interferon- $\beta$  in that it is not glycosylated and has serine substituted for the cysteine residue at amino acid position 17. It is indicated for use in ambulatory patients with relapsing-remitting MS to reduce the frequency of clinical exacerbations.<sup>14</sup> Although the overall mechanisms by which IFN $\beta$ -1b exerts its actions are unknown, it is believed to bind to the same cell surface receptor as interferon-alpha and natural interferon- $\beta$ .<sup>15</sup> It induces the expression of a number of proteins, via transcription factors, that mediate its immunologic, antiproliferative, and antiviral effects.<sup>16</sup> The immunomodulatory effects of IFN $\beta$ -1b are believed to play the major role in reducing the number and frequency of exacerbations in patients with MS.<sup>16,17</sup>

A double-blind, randomized, placebo-controlled, multicenter phase III trial was conducted in which 372 patients with relapsing-remitting MS received placebo (n = 123) or either 1.6 million IU (n = 125) or 8 million IU (n = 124) of IFN $\beta$ -1b subcutaneously, every other day, for 2 years.<sup>18,19</sup> Eligibility criteria included clinically evident MS of at least 1 year's duration and at least two exacerbations in the 2 years preceding the trial without an exacerbation in the preceding month. Other inclusion criteria were an EDSS score of 5.5 or less (ambulatory without aids) and clinically stable disease at study entry. Patients who had received previous immunosuppressant therapy were excluded, and those needing more than



three brief courses of corticosteroids during a 12-month period were withdrawn from the study. At the end of 2 years, 80% of patients remaining in the study elected to continue treatment under double-blind conditions. Some patients were treated for as long as 5½ years.

After 2 years of treatment, the annual exacerbation rates in patients who received placebo or 1.6 million or 8 million IU IFNβ-1b were 1.27, 1.17, and 0.84 per year, respectively. The lower rate in the group given 8 million IU represents a 34% decrease from the placebo exacerbation rate and is highly significant ( $P = .0001$ ). After 3 years, the exacerbation rate in the high-dose group (0.84) compared with that in the placebo group (1.21) was still significantly reduced ( $P = .0004$ ).<sup>18</sup>

There was also a significant difference in the proportion of exacerbation-free patients among the treatment groups. After 2 years, the percentage of patients without exacerbations in the 8 million IU IFNβ-1b group (31%) was almost twice that in the placebo group (16%) ( $P = .007$ ). At 3 years, 22% of patients in the high-dose group were exacerbation free, compared with 14% in the placebo group, but the difference was no longer statistically significant ( $P = .097$ ).<sup>18</sup>

Serial annual MRIs showed no significant progression in lesion burden in the 8 million IU IFNβ-1b group in each successive year, whereas there was a highly significant increase in lesion area in the placebo group ( $P = .0001$ ).<sup>19</sup>

Of the 124 patients who received IFNβ-1b therapy at the recommended dose of 8 million IU every other day during clinical trials, 76% reported a flu-like symptom complex.<sup>14</sup> Over 3 years, the incidence of these events declined, with only 4% of patients experiencing the complex during the last 6 months. Other common adverse clinical and laboratory events associated with IFNβ-1b therapy include injection site reactions and menstrual disorders. The former are generally mild, but in approximately 5% of patients, skin necrosis may occur. This has occasionally required surgical treatment. Absolute neutrophil count less than 1,500/mm<sup>3</sup>, white blood cell count less than 3,000/mm<sup>3</sup>, and AST and ALT levels greater than 5 times baseline value may occur on occasion.<sup>14</sup> Neutralizing antibodies to IFNβ-1b developed in 27% of patients in the 8 million IU group in year 1, 6% of patients in year

2, and 2% in year 3; antibody positivity, which was sporadic in some patients and sustained in others, was associated with an increased exacerbation rate comparable to that in the placebo group.<sup>19</sup>

The approval of IFNβ-1b has had a noticeable effect on patients with MS and their families, neurologists, and clinical investigators and has brought about a new sense of therapeutic optimism.<sup>20</sup>

A second recombinant interferon-β, IFNβ-1a (Avonex), a natural sequence, glycosylated IFN-β produced in Chinese hamster ovary cells, is now marketed for the treatment of relapsing MS. IFNβ-1a also has been tested in a phase III randomized, placebo-controlled, double-blind multicenter trial, in which 301 patients received placebo ( $n = 143$ ) or 6 million IU IFNβ-1a ( $n = 158$ ) intramuscularly, once a week for 2 years.<sup>21</sup> In contrast to the IFNβ-1b phase III trial, the primary outcome measure in the IFNβ-1a trial was progression of disability rather than exacerbation rate. Progression of disability was measured by the time taken for an increase to occur in the EDSS score of 1.0 unit above baseline persisting for at least 6 months. Secondary outcome measures included time to first exacerbation, exacerbation rate, proportion of patients remaining exacerbation free, and change in disease burden as measured by MRI.<sup>21</sup>

Time to sustained progression of disability was significantly greater in the IFNβ-1a group than in the placebo group ( $P = .02$ ).<sup>21</sup> The proportion of patients with progression of disability at 2 years was 21.9% in the IFNβ-1a group compared with 34.9% in the placebo group.<sup>21</sup> In addition, patients receiving IFNβ-1a had one third fewer exacerbations and a significant reduction in the number of lesions as detected by gadolinium (Gd)-enhanced MRI, as compared with placebo.<sup>21-23</sup>

As in the IFNβ-1b clinical trial, the most frequent adverse effects in patients receiving IFNβ-1a were flu-like symptoms, injection site reactions, and menstrual disorders. However, in contrast to IFNβ-1b, local skin irritation and necrosis do not occur. Serum neutralizing anti-IFN activity was observed in 14% of patients receiving IFNβ-1a at week 52, in 21% of patients at week 78, and in 22% of patients at week 104; the majority of patients remained positive for neutralizing activity on repeat testing.<sup>21</sup> It is not yet clear whether this will affect clinical efficacy.



### Other Interferons

Early clinical trials of both natural and recombinant IFN- $\alpha$  in patients with MS were not too promising.<sup>17</sup> This is surprising, since both IFN- $\beta$  and IFN- $\alpha$  bind to the same cell surface receptor and have similar immunoregulatory functions.<sup>16</sup> It is possible that the relatively small doses and the frequency and route of administration used in the early trials were suboptimal. A recent 6-month randomized, double-blind, placebo-controlled pilot trial involving 20 patients with relapsing-remitting MS had more promising results.<sup>24</sup> Patients receiving 9 million IU of IFN $\alpha$ -2a (Roferon-A) intramuscularly every other day for 6 months had a significant reduction in exacerbation rate ( $P < .03$ ), and a higher proportion remained exacerbation free ( $P < .02$ ) compared with the placebo group. In addition, the median time to first exacerbation was approximately twice as long in the IFN $\alpha$ -2a group as in the placebo group (111 days versus 58 days).<sup>24</sup> MRI studies done before and after treatment revealed only one active lesion in the IFN $\alpha$ -2a group compared with 27 lesions in the placebo group—a significant difference ( $P < .01$ ). Thus, the MRI data verified the clinical information regarding the benefits of IFN $\alpha$ -2a treatment.<sup>24</sup>

As with all interferon compounds, IFN $\alpha$ -2a caused moderate side effects, mainly a flu-like complex and some mild laboratory abnormalities similar to those observed with IFN $\beta$ -1a and IFN $\beta$ -1b.<sup>19,21,24</sup> IFN- $\gamma$  has also been tested in clinical trials of MS, but it causes significant increases in disease activity.<sup>17</sup>

### Corticosteroids and Corticotropin

These compounds are thought to exert their beneficial effect in MS by reducing abnormalities in the blood-brain barrier, decreasing edema, improving axonal conduction, reducing intrathecal immunoglobulin G synthesis, and inducing immunosuppression by the steroid-mediated blockade of cytokine gene expression.<sup>20</sup> Despite their established role in managing exacerbations of MS, the use of corticosteroids and corticotropin (ACTH) to prevent acute attacks and favorably alter disease progression has not been thoroughly investigated.<sup>20</sup> Early trials showed that neither low doses of oral prednisolone<sup>25</sup> nor intramuscular ACTH<sup>26</sup> had any benefits after 18 months of treatment when compared with placebo.

In one study, Compston and colleagues<sup>27</sup> concluded that a short course of high-dose

IVMP, frequently used to treat the exacerbations of MS, did not have a prolonged effect on the immunologic abnormalities associated with the disease and thus had no long-term therapeutic value in patients with relapsing-remitting or chronic-progressive MS.

However, a recent study by the Optic Neuritis Study Group to evaluate the effect of corticosteroid therapy on the development of definite MS in patients treated for optic neuritis, often the first manifestation of MS, had a positive outcome.<sup>28</sup> Within 2 years, definite MS developed in 7.5% of patients treated with 1,000 mg of IVMP for 3 days and in 16.7% of those in the placebo group, a statistically significant difference ( $P = .006$ ).<sup>28</sup> Interestingly, the beneficial effect of IVMP occurred most in patients at greatest risk for developing clinically definite MS, as judged by the multifocal lesions seen on their MRI scans.<sup>28</sup> This study may encourage clinicians to administer IVMP for the first episode of optic neuritis, or any other neurologic abnormality that might signal the onset of MS, in an attempt to favorably alter the course of the disease.<sup>29</sup> In patients whose MS has progressed further, corticosteroids may be most valuable when they are used in conjunction with other immunologic agents.<sup>27</sup> In patients with progressive MS, IVMP did not seem to affect the natural progression of the disease.<sup>30</sup>

In addition to this study, a 2-year clinical trial comparing the relative benefits of bimonthly pulses of 10 mg versus 500 mg of IVMP is now in progress, and a separate study comparing the benefits of IVMP and IFN $\beta$ -1b is being planned.<sup>20</sup> There is evidence from one study<sup>30</sup> that 1,000 mg of IVMP daily for 10 consecutive days significantly reduced the relapse rate over an average of 2.6 years in patients with relapsing-remitting or progressive-relapsing MS (compared with rates 1 year before study entry [ $P < .0001$ ]).

### Azathioprine

Azathioprine, a purine analogue that suppresses cell-mediated hypersensitivity reactions and alters antibody production,<sup>20</sup> has been used in clinical trials of patients with MS. Results of 22 such trials have been published.<sup>20</sup> Seven of these, two single-blind and five double-blind studies, were reviewed in a meta-analysis by Yudkin et al.<sup>31</sup> This analysis evaluated data from 793 patients with relapsing-remitting, progressive, or progressive-relapsing MS, 459 of whom had been treated for at least 3 years.<sup>31</sup> Mean



changes in Kurtzke disability scores, reported in six of the trials, indicated increased neurologic impairment after 1, 2, and 3 years; although the degree of neurologic impairment was less than that observed in the control groups, it was not statistically significant.<sup>31</sup> Azathioprine significantly reduced the risk of relapse, and the probability of remaining disease free was 1.51, 2.04, and 1.97 times greater after 1, 2, and 3 years, respectively. However, adverse effects were common in treated patients and included leukopenia, anorexia, diarrhea, vomiting, abdominal pain and other gastrointestinal disturbances, abnormal liver function, and skin rash.<sup>31</sup> Despite lingering concerns that cancer may develop after long-term administration, this association has not been substantiated.<sup>32</sup>

Although azathioprine remains an investigational agent for the treatment of MS and its clinical benefit appears to be modest, it is the most commonly used form of immunosuppressant therapy for this disease.<sup>20</sup> It is probable that azathioprine will continue to have a limited role in the management of patients with MS because of its relatively acceptable toxicity, favorable cost, and comparative ease of administration.<sup>20</sup>

#### *Cyclophosphamide*

Administration of cyclophosphamide, an alkylating agent with cytotoxic as well as immunosuppressive effects, reduces the numbers of helper T cells and suppressor T cells. This reduction is more pronounced in the former.<sup>20</sup>

Many trials have confirmed that the clinical benefits of cyclophosphamide therapy for MS are restricted to the short term and are marginal at best, with toxicity being a major problem.<sup>20</sup> Acute toxicity includes nausea and vomiting, alopecia, hemorrhagic cystitis, and myelosuppression, whereas long-term toxicity may involve induction of leukemia or bladder cancer. Accordingly, cyclophosphamide is an unlikely candidate for long-term therapy for patients with MS.<sup>33,34</sup> However, a recent study in which patients with MS were given pulse IV cyclophosphamide therapy in combination with monthly IVMP suggested a clinical benefit due to a shift from a Th1-type to a Th2-type cytokine profile (IFN- $\gamma$ , lymphotoxin versus IL-4, IL-5).<sup>35</sup>

#### *Cyclosporine*

Cyclosporine (cyclosporin A), which is widely used to prevent graft rejection after

organ transplantation, is an immunosuppressive agent with a relatively specific, but reversible, inhibitory effect on helper T cells.<sup>7,36</sup> Since preliminary reports have shown that cyclosporine can modify the course of experimental allergic encephalomyelitis in animals and may have value in the treatment of other autoimmune diseases in humans, its possible therapeutic role in MS has been investigated.<sup>36</sup>

The Multiple Sclerosis Study Group conducted a placebo-controlled, double-blind trial of 554 patients with progressive MS in which 273 patients received a daily dose of oral cyclosporine for 2 years.<sup>36</sup> Patients in the treatment group had a statistically significant delay in disease progression, but the clinical effects of treatment were slight. Furthermore, the nephrotoxicity and hypertensive effects of the drug outweighed its benefits. Adverse effects were also a cause for concern in a multicenter, double-blind, randomized trial of cyclosporine versus azathioprine involving 194 patients, the majority of whom had relapsing-remitting MS.<sup>37</sup> No significant differences in exacerbation rates or disability progression were shown over 2 years, and more than twice as many side effects were reported in the cyclosporine group as in the azathioprine group.

#### *Methotrexate*

Because of its anti-inflammatory and immunomodulatory actions, in addition to its beneficial effect in rheumatoid arthritis, another autoimmune disease, methotrexate is now under investigation for the treatment of progressive MS.<sup>38</sup> In a double-blind, placebo-controlled phase II study, 60 patients with an EDSS score of 3.0 to 6.5 received weekly placebo or 7.5 mg of oral methotrexate. A composite of outcome measures reflecting both upper and lower extremity function was used to measure efficacy of treatment. At the end of the 2-year study period, progression of neurologic impairment was significantly less in the group given methotrexate ( $P = .011$ ), and adverse effects were minimal.<sup>38</sup>

#### *Roquinimex*

The synthetic immunomodulator roquinimex (Linomide) has shown promise in patients with relapsing-progressive MS. Roquinimex increases natural killer cell activity and stimulates other lymphocyte subpopulations.<sup>39</sup> It also interferes with antigen presen-

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