KEY POINT:

- The treatment of acute exacerbations of MS has centered on use of corticosteroids or adrenocorticotropic hormone.

TREATMENTS FOR MULTIPLE SCLEROSIS

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ABSTRACT

The field of multiple sclerosis entered the treatment era in 1993, over a decade ago, and now enjoys the availability of five marketed disease-modifying agents. This is an enviable position, not yet obtained in most other serious neurologic diseases. Despite this, the current agents provide only a modest benefit, and improvements in therapeutic options will be welcome. Therapy of multiple sclerosis centers on immunomodulation and immunosuppression, in keeping with the known immunoregulatory abnormalities in this illness. Treatment consists primarily of use of corticosteroids for acute exacerbations and for disease modification, either interferon or glatiramer acetate. More severe disease can be treated with mitoxantrone. Other agents have been utilized, but the basis for their use is less compelling.

Treatment of multiple sclerosis (MS) can be divided into three types: treatment of acute exacerbations, disease-modifying therapies, and symptomatic therapies. For this chapter, we will discuss the first two. Symptomatic therapies are discussed in a separate chapter.

TREATMENT OF ACUTE EXACERBATIONS

The treatment of acute exacerbations of MS has centered on use of corticosteroids or adrenocorticotropic hormone (ACTH). Few well-designed, controlled studies on steroid use have been done since the initial study by Rose and colleagues in 1970. In that study, patients treated with ACTH administered intramuscularly (IM) over 2 weeks, beginning at 80 units daily, improved more rapidly than those treated with placebo. The beneficial effect was only evident for a few weeks, however, with no long-term difference seen between the two groups, as a proportion of patients will recover some degree of function spontaneously after an acute attack. Subsequent studies have utilized intravenous methylprednisolone (IVMP). Although none of these studies are considered pivotal, they suggested a short-term benefit from steroid. While there are little data to recommend one form of corticosteroid over another or the optimal dosing schedule, most centers utilize a 3- to 5-day course of IVMP 1 g daily, optionally followed by a short course of rapidly tapered oral prednisone. A meta-analysis of three studies comparing the effect of intravenous (IV) high-dose steroid to placebo on recovery using the Expanded Disability Status Scale (EDSS) confirmed the benefit of high-dose steroid when assessed up to 28 days after treatment (Miller et al, 2000). The same study evaluated two dose-testing regimens and could not find a short-term difference between high-dose and low-dose steroids. Approximately 85% to 92% of patients improve with IVMP versus 33% to 40% of controls after 1 week of therapy (Durelli et al, 1985). Another meta-analysis looked at a number

of steroid trials during acute exacerbations and found that the data supported an effect of steroids on short-term improvement but could not substantiate an effect on long-term outcome or subsequent relapse rate reduction (Brusaferri and Candelise, 2000).

A study of an adhesion molecule blocker (see below), in which there was a placebo group and a group that received IV methylprednisolone 1 g/d for 3 days demonstrated that methylprednisolone was significantly better than placebo (or the adhesion molecule blocker) at reducing measures of disability and impairment. This effect persisted through at least 90 days (**Figure 6-1**). The safety of using oral steroids, in moderate doses (60 mg/d to 100 mg/d) was a concern following the Optic Neuritis Treatment Trial, where an increased frequency of recurrent optic neuritis was seen in the oral steroid–treated group. These results have neither been confirmed nor refuted by additional studies.

It is not clear whether equivalent doses of oral steroids are as beneficial as those given intravenously. In one study, 35 patients in relapse were treated with either IV or oral methylprednisolone, 500 mg/d for 5 days. No difference was found in EDSS at day 5 or day 28 after treatment. However, patients were entered up to 4 weeks after onset of their relapses (Alam et al, 1993). In another study, using unequal dosing, 42 patients were treated with oral methylprednisolone 48 mg/d for 7 days, followed by 24 mg/d for 7 days, and then 12 mg/d for 7 days, while 38 patients were treated with IVMP 1 g/d for 3 days. There was no significant difference in EDSS at 4 weeks. Again, patients were entered within 4 weeks of the onset of their relapses (median duration from onset of symptoms was 13 days in the IV group and 8.5 days in the oral group) (Barnes et al, 1997). Sellebjerg and colleagues studied the effect of oral methylprednisolone 500 mg/d for 5 days followed by a taper as treatment of relapses seen within 4 weeks (Sellebjerg et al, 1998). In this randomized, placebo-controlled, blinded trial of 51 patients, those treated with high-dose oral steroids did better than placebo on EDSS and Scripps score when assessed up to 8 weeks after therapy. Side effects were modest and tolerable. The authors suggested that the advantage of IVMP was due to the doses employed rather than the route. The tolerability of high-dose oral steroids has been assessed by Sellebjerg and colleagues (1998) and Metz and colleagues (1999). Sellebjerg found that oral methylprednisolone 500 mg/d for 5 days was well tolerated. Gastrointestinal symptoms (mostly heartburn), insomnia, and hot flashes were significantly more common in the steroid-treated group. Most adverse events were mild, and none were serious. Metz and colleagues reported on the tolerability of treating 21 patients (15 oral, 6 IV) with either 1250 mg/d of

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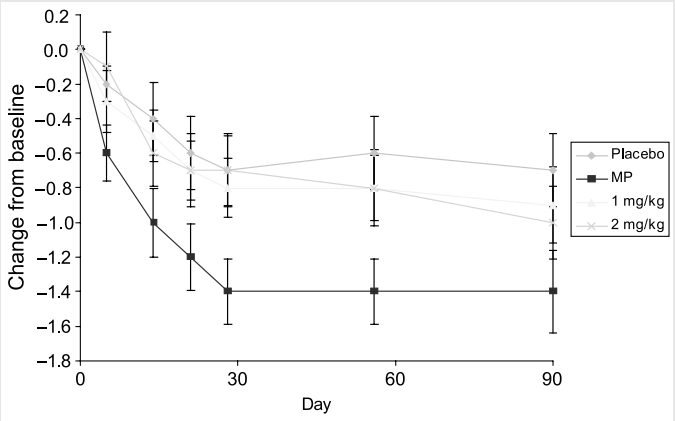

FIGURE 6-1

Change in EDSS from onset of an exacerbation. Treatment with intravenous steroid had an immediate and prolonged effect.

EDSS = Expanded Disability Status Scale; MP = methylprednisolone.

KEY POINTS:

- Problems with prior oral and IV steroid reports center on the fact that patients were entered into the studies up to 8 weeks after onset of an exacerbation.
- The importance of treating acute exacerbations was highlighted by an analysis of the placebo groups from several of the recent clinical trials of disease-altering therapies. A measurable worsening of both scores was apparent within 3 months after the exacerbation and persisted through subsequent study visits.

oral prednisone in 2 divided dosages on alternate days for 5 doses or 1000 mg IVMP infused on alternate days for 5 doses. All received an 18-day oral prednisone taper starting at 60 mg/d. Both therapies were well tolerated and produced similar side effects. The commonest were (in descending order of frequency) insomnia, heartburn, weight gain/edema, mood change, headache, and urinary frequency. Specific tests for gastric permeability revealed modest increases for both treatments and less than occurs with 2 doses of aspirin.

Problems with prior oral and IV steroid reports center on the fact that patients were entered into the studies up to 8 weeks after onset of an exacerbation. This is likely too long a delay after onset and thus includes patients who are already undergoing spontaneous recovery, potentially masking a therapeutic difference in treatments. Further, no study has adequate numbers of patients to reach a statistically valid conclusion regarding the efficacy of oral versus IV therapy. Additionally, the IV and oral doses have not been comparable in that the dose for each route of administration has not accounted for the factors that lead to a difference of plasma levels. Approximately 80% of orally ingested methylprednisolone is absorbed from the gastrointestinal tract to the plasma, but at higher doses only 50% to 60% may be absorbed.

A multicenter, randomized, blinded clinical trial comparing 1 g of IVMP to 1.4 g of methylprednisolone orally for acute exacerbations evaluated within 7 days of onset is currently in progress.

The importance of treating acute exacerbations was highlighted by an analysis of the placebo groups from several of the recent clinical trials of disease-altering therapies (Lublin et al, 2003). As the patients were followed with assessments every 3 months, one could gauge the effect of an acute attack on measures of neurologic function, ie, EDSS and Scripps score. The analysis revealed that a measurable worsening of both scores was apparent within 3 months after the exacerbation and persisted through subsequent study visits. For the EDSS, residual deficit was seen in 42% of all

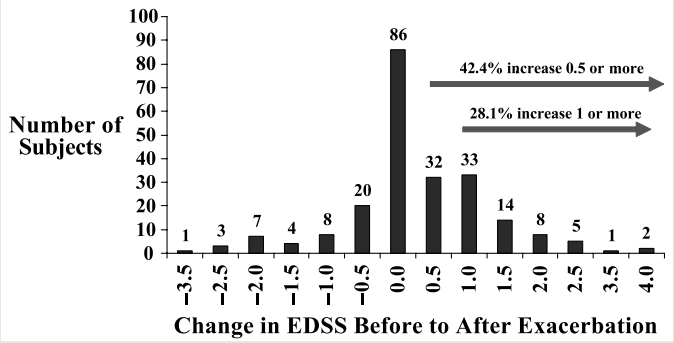

FIGURE 6-2 Residual deficit measured from before to after an acute exacerbation.

EDSS = Expanded Disability Status Score.

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exacerbations, with a mean residual worsening of 0.27 EDSS points (**Figure 6-2**). For the Scripps score, residual deficit was seen in 50% of patients, with a mean residual worsening of 1.1 points. When one looks at those exacerbations that produced measurable deficit during the flare-up, the numbers are even more impressive, with 57% having residual deficit of 0.57 EDSS units. These results provide compelling data that relapses are detrimental and that incomplete recovery from relapses is an important cause of accrued disability. Therefore, therapies that reduce relapse rate may be beneficial, independent of their ability to affect the progressive aspect of this illness.

The use of adhesion molecule blockers was a theoretically attractive approach to treating acute exacerbations, in the hope that by blocking trafficking of lymphocytes into the central nervous system (CNS), one could lessen the effects of an acute attack. Two trials attempted to utilize this approach. The first employed a monoclonal antibody directed against CD11/CD18 in an attempt to block LFA1 on lymphocytes as well as adhesion molecules on macrophages and neutrophils. Patients were treated with either 1 of 2 doses of the monoclonal antibody, methylprednisolone 1 g/d for 3 days, or placebo, with provisions for a steroid rescue. Treatment had to be initiated within 7 days of the acute attack. The results did not demonstrate any effect of the adhesion-blocking agent, but demonstrated that IVMP produced a significantly better outcome than placebo (or the monoclonal antibody) that persisted through at least 90 days (**Figure 6-1**). Based on animal studies demonstrating an amelioration of experimental autoimmune encephalomyelitis, a second study employed natalizumab, a monoclonal antibody directed against the integrin VLA-4 on lymphocytes. In this study, patients were entered within 96 hours of the acute exacerbation. This study also failed to demonstrate a beneficial effect from blocking adhesion molecules. These results suggest that at the time an acute exacerbation becomes clinically apparent it is too late to attempt to block the entry of cells into the CNS. Alternatively, the entire approach may be wrong. Additional studies are underway to determine if more chronic therapy with adhesion molecule blocking agents will affect the course of MS (see discussion of natalizumab below).

Plasmapheresis

Plasmapheresis has no known role in altering the long-term clinical course of MS. However, there is good evidence that plasmapheresis may improve recovery from an attack of severe inflammatory demyelination, as occurs in MS, if steroids fail. One study demonstrated significant functional improvement in 42% of patients treated with plasmapheresis who had failed to respond to IV corticosteroids (Weinshenker et al, 1999).

DISEASE-MODIFYING THERAPIES

Over the past 11 years, the field of MS therapeutics has evolved from one that offered no disease-modifying therapies to the present, where five approved agents, representing three different classes of drugs, are available (Hartung et al, 2002; IFNB Multiple Sclerosis Study Group, 1993; Jacobs et al, 1996; Johnson et al, 1995; PRISMS Study Group, 1998). The development of these agents has been based on our understanding of the immunopathogenesis of MS, and, almost paradoxically, the results of some clinical trials have caused a rethinking of aspects of immunopathogenesis

KEY POINTS:

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- Over the past 11 years, the field of MS therapeutics has evolved from one that offered no disease-modifying therapies to the present, where five approved agents, representing three different classes of drugs, are available.

KEY POINT:

- Based on study results, the field has moved from the cautious skepticism that greeted the publication of the first successful large-scale clinical trial of an MS disease-modifying agent in 1993 to a more ready acceptance of the utility of the several carefully studied, approved, and available disease-modifying agents in relapsing-remitting MS and even in clinically isolated syndromes.

The initial successful clinical trials in MS were in established, active, relapsing-remitting (RR) MS. Subsequent trials targeted secondary progressive (SP) MS, with less impressive and less consistent results (Cohen et al, 2002; European Study Group, 1998; Secondary Progressive Efficacy, 2001). The field of MS therapeutics was pushed further along with the successful outcome of two trials of patients with clinically isolated syndromes, ie, first attacks consistent with demyelinating disease that do not meet the criteria for definite MS (Comi et al, 2001a; Jacobs et al, 2000).

Based on these results, the field has moved from the cautious skepticism that greeted the publication of the first successful large-scale clinical trial of an MS disease-modifying agent (DMA) in 1993 to a more ready acceptance of the utility of the several carefully studied, approved, and available DMAs in RRMS and even in clinically isolated syndromes.

Interferon Beta-1b

The first study to demonstrate the effectiveness of systemically administered interferon beta (IFN-β) was the North American Interferon beta-1b (Betaseron) study, which started in 1988 (IFNB Multiple Sclerosis Study Group, 1993). This study utilized a double-blind placebo-controlled design. The inclusion criteria were patients with RRMS, Kurtzke EDSS scores of 0 to 5.5 and two or more exacerbations in the prior 2 years. Data were obtained from 372 patients randomized to receive placebo, 1.6 mIU IFN, or 8 mIU IFN, subcutaneously, every other day. The primary outcome measures were reduction in annual exacerbation rate and proportion of exacerbation-free patients. At the end of the planned 2-year study, patients were offered re-enrollment for an additional year to assess progression of disease, as measured by change in EDSS.

The results of this study, after 2 years, were that patients who received 8 mIU of IFN had a significant reduction, by almost one third, in the annual exacerbation rate, as compared with placebo-treated patients (0.84 versus 1.27; $P = 0.0001$). More importantly, the degree of reduction in exacerbation rate was most impressive, almost 50%, in those exacerbations rated as moderate or severe. The other primary end point, proportion of patients remaining exacerbation free, also showed a significant difference, favoring IFN (8 mIU IFN = 36, placebo = 18, $P = 0.007$). The median time to first exacerbation was significantly prolonged, nearly twice as long in the 8 mIU group as compared with placebo ($P = 0.015$). Further, there were significant reductions in the number and days of hospitalization and need for steroids in the IFN-treated group. The IFN 1.6 mIU group demonstrated a dose-response effect, with clinical values between that of the 8 mIU group and the placebo group in most outcome measures.

The patients in this study had baseline and yearly magnetic resonance imaging (MRI) scans that were centrally analyzed in blinded fashion. MRI activity was assessed by measuring new or enlarging lesions in a subset of 52 patients who had scans every 6 weeks for 2 years. MRI activity was reduced in the IFN 8 mIU treatment group by 80% compared with the placebo group ($P = 0.0062$). The rate of new lesions, active lesions, and number of patients free of new lesions all significantly favored the IFN 8 mIU group. MRI lesion burden, measured on T2-weighted images, was significantly less at 2 years in the treatment group ($P < .001$).

By the time all enrolled patients had completed 3 years on protocol, the total data set for the blinded

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