Chapter 2

Treatment for an Acute Exacerbation

OVERVIEW

At least 80 to 85 percent of people with MS have an acute period of worsening (also called an exacerbation, bout, attack, or relapse) at some time. One of the most commonly used definitions of an exacerbation is the [sub] acute appearance of a neurologic abnormality that must be present for at least 24 hours in the absence of fever or infection. A wide variety of symptoms can occur during exacerbations. MRI scans taken at such times often show new active (gadolinium-enhancing) lesions in the brain or the reactivation or enlargement of old lesions.

Whereas quite some evidence points to the fact that exacerbations are the result of focal areas of inflammation in the CNS, little is known about what initiates exacerbations and which processes determine the level of recovery. Many studies have shown that there is an increased risk of exacerbations in the first 4 weeks after a systemic infection and that exacerbations following a systemic infection lead to more sustained damage than other exacerbations. There also seems to be a rather consistent association between stressful life events and subsequent exacerbations, but the identification of specific stressors so far
has been unsuccessful. Another precipitating factor that has been identified is the early postpartum period.

A recent analysis of relapses that occurred in patients who were part of the placebo arm of clinical trials showed that 2 months after the initiation of a relapse about one-third of patients still had some measurable residual deficit.

Although most relapses remit spontaneously, many clinicians advise treatment for the relapses that have significant functional impact.

Corticosteroids have been the mainstay of treatment for the management of acute relapses for many years. They have immunomodulatory and antiinflammatory effects that restore the integrity of the blood–brain barrier, reduce edema, and possibly facilitate remyelination and improve axonal conduction. Corticosteroid therapy has been shown to shorten the duration and severity of the relapse and accelerate recovery, but there is no convincing evidence that the overall degree of recovery is improved or that the long-term course of the disease is altered.

Adrenocorticotropic hormone (ACTH, corticotropin) was the first agent demonstrated to be helpful in recovery from acute exacerbations. Brief courses of high-dose intravenous (IV) methylprednisolone (IVMP, 500–1000 mg/day for 3–5 days) have generally supplanted ACTH because of convenience, reliability, fewer side effects, and perhaps a more consistent and rapid onset of action.

Results of the Optic Neuritis Treatment Trial have been extrapolated by many neurologists to MS-associated relapses in general. In this study, 457 patients with acute optic neuritis were randomly assigned to receive 1000 mg of IVMP per day for 3 days followed by 1 mg of oral prednisone per kilogram per day for 11 days, 1 mg of oral prednisone per kilogram per day for 14 days, or oral placebo. The advantage of studying cases of optic neuritis is that very sensitive outcome measures (e.g., visual field, contrast sensitivity, color vision, and visual acuity) can be applied. The rate of recovery of vision was significantly faster in the IVMP-treated group, with the greatest benefits in patients
with visual acuity of 20/40 or worse at entry. After 6 months there was no significant difference in visual acuity between the IVMP and placebo groups. Oral prednisone provided no benefit over placebo.

Unanticipated findings were that during the 6 to 24 months of follow-up, the risk of recurrent optic neuritis in either eye was increased with oral prednisone and that IVMP reduced by approximately 50 percent the risk of a new attack leading to the diagnosis of MS. This effect was most evident for patients at highest risk for subsequent relapse, that is, those with multiple brain lesions on MRI at entry into the study. These results should be interpreted with the understanding that this study was not designed to assess the effect of glucocorticoids on subsequent relapses and that the IVMP group was unblinded and lacked a placebo control. Differences between the treatment groups were no longer significant after 3 years, which suggests that IVMP at best delayed but did not stop the development of MS.

Magnetic resonance imaging follow-up studies have convincingly shown the effect of steroids, as evidenced by the reduction of gadolinium-enhancing lesions. However, this effect is only short-lived, and new enhancing lesions can develop within a week following treatment.

Despite the widespread use of corticosteroids as a treatment for relapses, very little is known about the optimal treatment regimen. The main controversies relate to the relative efficacy of the type of steroid (i.e., intramuscular ACTH versus IV steroids versus oral steroids), the optimal dosage for each route of administration, and whether a short course of IV treatment should be followed by a tapering regimen of orally administered corticosteroids.

Some clinicians substitute oral corticosteroid treatment for IVMP for the management of relapses mainly because of its easier route and reduced expense of administration. Data substantiating its equivalent benefit in acute relapse have been presented but are not very persuasive. Remarkably, in various studies—all being rather small—quite different dosage regimens of oral steroids have been applied.
Other antiinflammatory drugs, the so-called nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, indomethacin, ibuprofen, and naproxen, have not been shown to be of benefit in the treatment of MS relapses.

**Conclusion:** A short course of IVMP remains the intervention of choice in patients with an acute exacerbation that warrants treatment. Prospective evidence indicates that it diminishes acute neurologic dysfunction; an effect on the long-term course of the disease has not been firmly established. It is unclear whether an oral taper of steroids would add any benefit.

**SPECIFIC AGENTS**

**Intravenous Methylprednisolone**

As noted previously, it is common practice to employ a short course of corticosteroids to treat acute relapses of MS. Of the various approaches applied, the administration of IV methylprednisolone (IVMP) has become the most popular, especially because it can be given as a short course (typically 3–5 days), has a rapid onset of action, and is associated with relatively few side effects. Its use is now common practice in many clinics and hospitals on an outpatient basis. It should be given only under medical supervision because side effects, even though extremely rare, include psychosis, peptic ulceration, aseptic bone necrosis, infections, cardiac arrhythmias, and thrombo-embolism.

Some neurologists also employ periodic pulses of IVMP (e.g., once monthly) in patients with progressive MS, but there is no firm evidence that this has a favorable impact on the course of the disease, and there is an increased risk of side effects.

*In the opinion of the Committee, a course of corticosteroids can be recommended for patients with exacerbations who have significant functional impact. Long-term use may be associated with significant serious side effects.*
Intravenous Dexamethasone

Dexamethasone is another corticosteroid that shares many characteristics with methylprednisolone. Although the number of patients with MS exacerbations being treated with IV dexamethasone is substantially smaller than that being treated with IVMP, there is some evidence that its effects are comparable when given as a short course. In many countries its cost is substantially lower than that of IVMP.

In the opinion of the Committee, it is difficult to give a recommendation in the absence of carefully performed studies, but intravenous dexamethasone may represent a less expensive alternative to treatment with intravenous methylprednisolone.

Intramuscular Adrenocorticotropic Hormone

Thirty-five years ago, short-term intramuscular (IM) adrenocorticotropic hormone ACTH given daily in high doses was shown to reduce the severity and shorten the duration of exacerbations. In more recent studies, claims have been made that IVMP works more quickly and effectively than ACTH, and most neurologists now prefer this treatment.

In the opinion of the Committee, intramuscular ACTH, although proven efficacious, is no longer the preferred treatment for MS exacerbations.

Oral Steroids

There is conflicting evidence regarding the efficacy of oral steroids in the treatment of exacerbations. In the optic neuritis study referred to previously, there were more relapses in subsequent months in the oral prednisone group than in either the placebo-treated or the IVMP-treated group. Many people who have examined these data, however, reject the conclusion of the authors
that oral prednisone was responsible for the increased later exacerbation rate.

A Danish study demonstrated the efficacy of oral methylprednisolone (MP) as a treatment for exacerbations. It compared the effects of oral MP therapy and placebo in patients with an episode lasting less than 4 weeks. Twenty-five patients received placebo, and 26 patients were given 500 mg oral MP once a day for 5 days, followed by a 10-day drug tapering period. Patients receiving MP did consistently better than those receiving placebo. At 8 weeks after the start of treatment, 32 percent of patients in the placebo group had improved by one Expanded Disability Status Scale (EDSS) point, whereas 65 percent of patients taking MP had a similar improvement.

Another study, performed in the United Kingdom, compared oral MP with IVMP: 80 patients with MS were treated within 4 weeks of the start of an exacerbation. Of these patients, 38 received IVMP (1000 mg/day for 3 days) and 42 received oral MP (48 mg/day for 7 days, followed by 24 mg/day for 7 days and 12 mg/day for the final 7 days). Hence, the cumulative dose of methylprednisolone was 3000 mg in the IV group and 588 mg in the oral group. The primary outcome was the difference between the two groups in improvement in the EDSS score of at least one full point after 4 weeks. No significant difference was found either with respect to this primary outcome or in any other measurement at any stage of the study. The main concerns regarding this study are that there was only a modest effect of treatment in both arms and that therefore a statistical type II error (real difference not being detected) is quite likely to occur. One must remember in this respect that statistical methods are tools that are predominantly developed to detect differences rather than to prove similarities: the absence of proof of difference is not equal to the proof of absence of difference.

It is extremely important that oral treatment with steroids not be prolonged because the complications of long-term treatment are well established. Complications include generalized puffiness, “moon face,” psychosis, peptic ulceration, infections, and acne. Long-term use may even result in serious side effects,
such as fractures related to bone softening, aseptic necrosis of bone, cataracts, hypertension, and adrenal insufficiency.

*In the opinion of the Committee, treatment with oral steroids, even though it has recently gained some support, is not the preferred treatment for exacerbations, because only rather small studies (applying very different dosages) have been performed and it is not clear whether oral treatment, which in many regimens has to be prescribed longer than intravenous treatment, might increase the risk of side effects.*

Intrathecal Steroids

*In the opinion of the Committee, this therapy should not be used because of reported harmful effects.*

Aspirin (Sodium Salicylate) and Nonsteroidal Antiinflammatory Drugs (Indomethacin, Phenylbutazone, Naproxen, Ibuprofen, and Fenoprofen)

These drugs are widely used to reduce inflammation, especially in arthritis. Proper evaluation of this type of drug in MS has not been done. A small study, however, suggests that ibuprofen is safe, although not effective in reducing the volume of active MS lesions seen on MRI. Ibuprofen and aspirin are being used to reduce early flu-like side effects of interferon beta and appear to be safe for the relief of discomfort.

*In the opinion of the Committee, there appears to be no scientific basis for use of this therapy other than for the relief of early side effects associated with interferon therapy.*

Plasmapheresis

During plasmapheresis (plasma exchange, or PE), blood is removed from the patient, and the liquid plasma and the cells are
separated by centrifuge. The plasma (including many lymphocytes) is discarded and replaced by normal plasma or human albumin to avoid loss of protein and fluid. The “reconstituted” blood is then returned to the patient. This process may be repeated a number of times. It is believed that substances that can damage myelin and/or impair nerve conduction are removed in this way.

There remain numerous reports (most of them uncontrolled and reporting on only very small numbers of patients) that PE may be effective in fulminant acute syndromes of MS (or acute disseminated encephalomyelitis).

A randomized controlled trial was performed at the Mayo Clinic in the U.S.A. Thirty-six patients with recently acquired, severe neurological deficits resulting from attacks of inflammatory demyelinating disease, who failed to recover after treatment with IVMP, were treated with either plasma exchange or sham treatment. Moderate or greater improvement in neurological disability occurred during 8 of 19 courses of active treatment compared with 1 of 17 courses of sham treatment. Moderate or marked improvement was associated with the male sex, preserved reflexes, and early initiation of treatment. Successfully treated patients improved rapidly following treatment and the improvement was sustained.

*In the opinion of the Committee, this therapy should be considered for those rare cases that present with acute, fulminant symptomatology and do not respond to intravenous steroids.*

**Intravenous Immunoglobulin**

Intravenous immunoglobulin (IVIG) is pooled human IgG that is presumed to alter the immune system by various mechanisms (also see page 41). A small, randomized trial testing the efficacy of adding IVIG to IVMP in the treatment of relapses was performed in the Netherlands. A beneficial effect of IVIG could not be demonstrated.
In the opinion of the Committee, IVIG should not be added to IVMP in patients with an acute exacerbation.

Guide to Further Reading


