

Recommendations Regarding Corticosteroids in the Management of Multiple Sclerosis

The National Medical Advisory Board of the National Multiple Sclerosis Society, while recognizing that the factors that enter into a decision to treat are complex and best analyzed by the individual patient's neurologist, has adopted the following recommendations to provide guidance to clinicians, insurers, and policymakers regarding the appropriate use of corticosteroids in the management of MS, particularly when data are lacking or unclear. They are based on existing literature and expert opinion derived from clinical practice and experience. Evidence is cited where it exists, but many aspects of steroid management are not evidence-based. This document is intended as a resource for neurologists in clinical practice.

EXECUTIVE SUMMARY

Treatment with high-dose corticosteroids is the accepted standard of care for those relapses that clinicians determine are appropriate for short-term therapy. Although open issues remain, as noted below, the following recommendations are general guidelines for the treatment of relapses, and for the less common use, and less certain benefits, of corticosteroids as long-term intermittent pulse therapy.

Management of Relapses

- ◆ The most commonly used regimen is 500–1,000 mg intravenous methylprednisolone (IVMP) daily for 3–5 days with or without a subsequent tapering dose of oral steroids (most often prednisone) for 1–3 weeks. Specific decisions as to dosage, duration of treatment, and whether or not a taper is used, are based on the type of relapse and the clinician's judgment.
- ◆ Given the lack of comparative data showing that divided dosage might be preferable, and based on practicality and convenience for all concerned, intravenous steroids usually can be administered as a single daily dose. However, the option of divided doses should be reserved for use in some circumstances.

- ◆ Some evidence supports the use of comparable doses of oral corticosteroids in place of high-dose IVMP. A definitive clinical trial has not yet been conducted; therefore the choice of therapy should be based on the clinician's experience and best judgment.
- ◆ Low-dose oral steroids are not generally recommended for treatment of relapses because of the superior efficacy of higher doses. Nevertheless, some patients do recover quickly following 10–14 days of low-dose oral therapy and some physicians may prefer this approach in selected cases.
- ◆ In general, we recommend that the clinician treat major relapses as quickly as possible, but take a “wait and see” approach before deciding to treat minor relapses. Steroid treatment may still be useful if the patient is not seen until 1–2 months after the onset of symptoms, or if manifestations are still evolving, or recovery is incomplete.
- ◆ High dose steroid treatment for relapses may be safely administered to patients on disease-modifying therapies, including the interferons, glatiramer acetate, mitoxantrone and natalizumab, but they should be used with care and with appropriate monitoring.

Chronic Therapy of MS

- ◆ Chronic daily corticosteroids are *not* recommended for MS.
- ◆ Pulse therapy has been used as a single to multi-day treatment every few weeks to months, sometimes as an add-on to disease modifying therapies, and at doses comparable to those used to treat relapses. However, evidence to support this manner of use is much less convincing than for the therapies currently approved by the Food and Drug Administration (FDA) directed at modifying the course of MS.
- ◆ It has not yet been determined whether pulse steroids have an additive effect when given in combination with the interferons, glatiramer acetate, or other agents. A recently completed clinical trial (Avonex Combination Trial—ACT) showed favorable, though not statistically significant, trends in multiple clinical and MRI outcomes (Cohen, Calabresi, et al., 2007).

Side Effects

- ◆ Side-effects of corticosteroids are common, including GI symptoms and insomnia, but most are not serious when these agents are used judiciously. Patients with diabetes mellitus, peptic ulcer, labile hypertension, psychiatric disorders, and those taking warfarin sodium (Coumadin®) should be closely monitored during steroid therapy, as should patients at risk for the development of other serious side effects.

CORTICOSTEROID TREATMENT OF MS RELAPSES

Short courses of high-dose corticosteroids have been routinely used to treat acute MS relapses for many years. The first therapeutic advance in this area began with the use of adrenocorticotrophic hormone (ACTH) to stimulate the synthesis of corticosteroids (Rose et al., 1970). A number of studies support the concept that steroids accelerate recovery (Durelli et al., 1986; Beck et al., 1992; Sellebjerg et al., 1998; Brusaferrri and Candelise, 2000).

There is limited evidence that steroid therapy may reduce tissue damage and improve the degree of recovery, at least as determined by magnetization transfer imaging (Richert et al., 2001). However, most studies have found little difference in the ultimate degree of clinical recovery following a relapse (Beck et al., 1993; Brusaferri and Candelise, 2000). Despite the suggestion (Beck et al., 1993) that the risk of a subsequent relapse may be reduced, other studies do not support this, nor do they support any delay in time to the next relapse (Goodin, 1999; Brusaferri and Candelise, 2000).

The most commonly used dosage regimen is 500–1,000 mg of IVMP daily for 3–5 days, with or without a subsequent tapering dose of oral steroids for 1–3 weeks (Beck et al., 1992; Barnes et al., 1985). Within this range, the number of days of treatment may vary depending on the type and severity of relapse and the clinician's judgment with respect to the individual patient. Although it is not clear at this time whether lower or higher doses might be more useful, 1,000 mg daily can be recommended as suitable for most patients.

Intravenous steroids can be administered either as a single dose per day or in divided doses. It is unclear which (if either) approach is more effective. In the Optic Neuritis Treatment Trial (ONTT; Beck et al., 1992) divided dosage (250 mg IVMP q6h) was used. Once a day administration saturates steroid carriers and might lead to greater effect, but the clinical significance of these different dosing regimens is unknown. Also, the use of single or multiple infusions potentially has economic implications. Although existing data are inconclusive, the consensus of this Steroid Task Force is that a single daily dose is just as effective, more practical, and probably less costly than divided doses.

The need for an oral taper—usually of oral prednisone—and its optimal duration, if used, are uncertain. Existing data do not favor one approach or the other, and there is no real consensus as to their use. Tapers may ease the transition off steroids, and because of this some physicians use them routinely but, unlike the situation in systemic lupus erythematosus (SLE), it is unlikely that a taper makes any difference to overall outcome in MS. A taper should not be used if a patient previously experienced significant side effects to low-dose steroids, or if there are other reasons for withholding it, such as coexisting diabetes, that might be affected adversely by steroids. Tapers have not generally been used in major clinical trials.

The question of how soon after the onset of a relapse steroid treatment should be initiated is related to two separate issues: whether to treat a specific relapse immediately and how late into a relapse it is effective to treat. Timing depends on the nature of the relapse. For example, optic neuritis is generally treated with a 3-day course of steroids, as used in the ONTT, whereas more severe relapses are treated with 5-day, or even 7-day courses. In general, we recommend that the clinician treat a major relapse (one that is potentially disabling) as soon as possible, but taking a “wait and see” approach may be appropriate in many circumstances, especially when treating minor relapses (those that are purely sensory or cause no increase in disability).

Although the steroid most often used to treat relapses is IVMP, other options may also be appropriate. For example, comparable doses of IV dexamethasone could be substituted for IVMP. Although comparative trials have not been done, dexamethasone is a reasonable alternative if MP is unavailable, or for other reasons such as a previous allergic reaction to MP. Patients on dexamethasone may experience fewer overall side effects due to its relative lack of mineralocorticosteroid effects and

consequently lower sodium retention than seen with other steroids. Dexamethasone and MP have different affinities for glucocorticoid and mineralocorticoid receptors, which may result in differences in clinical efficacy. However, such differences are likely to be minor, and MP is therefore recommended as the drug of choice.

There has been recent renewed interest in using intramuscular or subcutaneous ACTH, the original treatment for relapse management (Rose et al., 1970). Although ACTH may have some theoretical advantages, it is more expensive than corticosteroids, generally has more side effects, and gives less consistent results. It may have a place in rare situations, as when IV infusion is impractical, or in cases where its positive effects on bone via stimulation of dehydroepiandrosterone (DHEA) and mineralocorticoids may be desirable.

High-Dose Oral Corticosteroid Therapy

There is evidence suggesting that oral regimens may also be effective and may actually have some advantages. Studies have reported that oral therapy is equivalent to intravenous administration in other inflammatory autoimmune disorders including asthma (Ratto et al., 1988) and rheumatoid arthritis (Smith et al., 1988). Equivalent doses of steroids can be administered orally and intravenously, absorption and bioavailability are comparable (Morrow et al., 2004) and the therapy is well tolerated (Metz et al., 1999). Oral therapy is more convenient for the patient, family, and clinician, and is less expensive than traditional intravenous therapy (Robson et al., 1998). Furthermore, comparable oral doses may be given twice a day with food to reduce the number of tablets to be consumed with each dose.

Several methods have been suggested for administering high dose oral steroids, although none has been adequately tested. Potential regimens include a 3–7-day course of oral methylprednisolone 1,000 mg, oral dexamethasone at a dosage of 176 mg/day, as 44 four-mg tablets, or oral prednisone 1,250 mg (Morrow et al., 2004). In the first large-scale clinical trial to address this issue, a dose of 1,400 mg of oral MP will be compared to 1,000 mg of IVMP, to allow for an estimated 70% absorption rate of the oral preparation.

Although, on the basis of several relatively small studies (Sellebjerg et al., 1998, 1999; Alam et al., 1993; Barnes et al., 1997), similar high-doses of PO and IV steroids seem to have similar therapeutic benefit in treating MS relapses, it would be more reassuring if this apparent equivalence were confirmed in a larger study population. Additionally, adequate studies have not yet been done to confirm the oral dose of each agent that is bioequivalent to 1,000 mg IVMP.

Patient reports are varied among those who have been treated with both regimens, with some preferring IVMP (often administered at home by a nurse), while others prefer oral therapy.

Side Effects of High-Dose Corticosteroids

Short courses of high-dose corticosteroids usually are safe and reasonably well-tolerated, but they do have numerous potential adverse effects. The most common, but usually not serious, adverse effects associated with short courses of IV or oral corticosteroids include insomnia, dysphoria,

anxiety, hyperglycemia, headache, myalgia, easy bruising, edema, palpitations, metallic taste, increased appetite, acne, flushing and gastrointestinal distress.

Although uncommon, several important adverse effects have occurred with short courses of corticosteroids, including anaphylaxis (extremely rare), various mental disturbances (e.g., manic psychosis, euphoria, or suicidal depression), avascular necrosis of bone (especially of the femoral head), hypokalemia, and gastrointestinal perforation. Exacerbations of pre-existing peptic ulcer disease, diabetes mellitus, and hypertension have also been reported. Patients in high risk groups should be tested for potential problems related to steroid treatment. For example, diabetics should have glucose testing, patients on warfarin sodium should have their International Normalized Ratio (INR) checked, those with liver disease should be monitored, and patients with hypertension should be treated cautiously. Daily blood glucose testing is recommended, as there have been rare instances in which patients without a history of diabetes have developed diabetic ketoacidosis while taking high dose steroids. There is a low risk of electrolyte imbalance, depending on which steroid is used as well as the dose and duration of therapy. Other known metabolic abnormalities should be monitored as deemed appropriate. The incidence of problems is small in patients with relapsing remitting MS, most of whom are relatively young and have few medical co-morbidities. The clinician's best medical judgment should be applied on an individual basis.

Repeated courses of high-dose steroids increase the risk of osteoporosis, cataracts, glaucoma, Cushingoid features, and suppression of inflammatory and immune responses, increasing the risk of opportunistic infections (Braunwald et al., 2001). Prolonged daily steroid therapy, even at low doses, carries similar risks and should therefore be avoided.

Low-Dose Oral Prednisone—Does It Have a Place in the Therapeutic Armamentarium?

In general, low-dose oral prednisone (approximately 1 mg/kg) is not considered to be as effective as either high-dose oral prednisone or high-dose IVMP. For example, in optic neuritis trials, high-dose IVMP seemed to produce a more rapid recovery of vision, although this was not significant at all time points (Beck et al., 1992). This trial also reported an increased rate of recurrent optic neuritis with oral prednisone, although this observation may be spurious (Goodin et al. 1999). Higher-dose therapy is used more often because there are better data demonstrating its efficacy. Nevertheless, some patients do recover quickly following 10–14 days of low-dose oral therapy and some neurologists prefer this approach in selected cases. It is, of course, impossible to determine if an individual patient would recover from a relapse spontaneously without steroid therapy, whether high or low dose.

LONG-TERM PULSE THERAPY

Pulse therapy is often used as a single or multi-day treatment (3–5 days) every few months (3–4 months), or as an add-on to disease modifying therapies at doses comparable to those used to treat relapses. In practice, it is used most often for people who are developing secondary progressive disease, who have failed other therapies, and before using mitoxantrone (Zivadinov et al., 2001).

Research to date has focused on whether long-term pulse IVMP therapy may delay the progression of brain atrophy or disability in patients with progressive disease. In summary:

- ◆ A 5-year, phase II clinical trial of IVMP in patients with RRMS (Zivadinov et al., 2001) demonstrated that prolonged treatment with pulsed IVMP slowed the rate of whole-brain atrophy, the development of destructive lesions (T1 black holes), and the development of sustained physical disability as compared to controls.
- ◆ Pulse IVMP prevented the development of brain atrophy in 11 patients with primary progressive MS (Pato-Pato et al., 2003).
- ◆ A small retrospective study of patients who had received monthly pulses of IVMP showed that the treatment was associated with improvement in fatigue, spasticity, and motor strength (Pirko and Rodriguez, 2004). No acute exacerbations occurred in 9 of 10 patients with PPMS or SPMS.
- ◆ Pulse IVMP has also been shown to prevent sustained disability. In a phase II study of 108 patients with SPMS, IVMP therapy was associated with a marginally significant delay in the onset of sustained disability (Goodkin et al., 1998).
- ◆ In contrast, a single course of IVMP during an attack of acute optic neuritis failed to prevent the development of optic nerve atrophy (Hickman et al., 2003).

Several studies have investigated the effect of glucocorticosteroids as an add-on to standard disease management therapy, and several multi-center combination trials have either been presented in preliminary fashion or are on-going:

- ◆ A recent study (Cohen et al., 2007) added steroids (IVMP 1,000 mg for 3 successive days every other month) to Avonex[®], and also evaluated the combination of Avonex, IVMP, and methotrexate. Data showed favorable, though not statistically significant, trends.
- ◆ Another double-blind controlled trial will evaluate the efficacy of IFN β -1b (Betaseron[®]) alone or in combination with bimonthly IVMP in secondary progressive MS patients.
- ◆ The ASSERT study is investigating the effect of IVMP plus Copaxone[®] versus Copaxone alone on brain atrophy in relapsing remitting MS patients.
- ◆ Several studies in Europe are investigating combinations of pulse IVMP with Rebif[®] (22 and 44 mg).

Treatment with repeated IVMP pulses was not associated with osteoporosis in patients with MS who participated in a phase II trial of pulsed use of IVMP over 5 years (Zorzon et al., 2005). However, osteopenia was observed more frequently in MS patients than in healthy controls. These data suggest that repeated pulses of IVMP given over a long period do not result in substantially increased risk of osteoporosis in MS patients. Moreover, osteopenia was found only in the control group, who had a significantly higher EDSS score than patients in the IVMP group, suggesting that decreased mobility may contribute to bone loss more than corticosteroid use.

STEROIDS AND DISEASE MODIFYING THERAPIES

Steroids have many metabolic effects (Barkhof et al., 1992; Sellebjerg et al., 2000; Elovaara et al., 1998; Gelati et al., 2002; Leussink et al., 2001; Rosenberg et al., 1996; Wandinger et al., 1998) and therefore many potential interactions and undesired side-effects.

The principal concern is their potential to interact with the disease-modifying agents to lower the threshold for opportunistic infections and other adverse events. However, all of the phase III pivotal trials of disease modifying agents have permitted the use of high dose IVMP to treat relapses, with no untoward side effects. Beta interferons synergize with steroids on MRI (Gasperini et al., 1998) to prolong their effect on suppression of gadolinium enhancing lesions, and high dose steroids may be used in combination with mitoxantrone without concern about serious adverse events (Edan et al., 1997).

Since steroids are immunosuppressive and prevent the migration of immune cells to the CNS, there is concern about a potentially negative synergy with Tysabri®. In the AFFIRM trial, steroids were administered for acute flares and no complications of this combination were observed. Nevertheless, in clinical practice, it is important to ensure, insofar as possible, that progressive multifocal leukoencephalopathy (PML) is not the cause of a suspected MS exacerbation during treatment with Tysabri. All patients receiving Tysabri must be enrolled in the FDA-mandated TOUCH™ surveillance program. In addition, an MRI scan should be considered before using steroids in this situation.

Our recommendation is that steroid treatment should not be avoided in patients on disease-modifying therapies, but they should be used with care and appropriate monitoring.

SUMMARY

Corticosteroids play an important role in the management of multiple sclerosis. Indications for the treatment of relapses are well established. Other indications, especially for the use of long-term intermittent pulse therapy, are less clear. Oral high dose steroids may be considered in place of IVMP in selected patients; however, IV therapy remains the standard of care at this time. The option of low dose oral treatment should also be retained for patients in whom this approach seems appropriate. Management may vary among patients and in the same patient at different times. It is important for the physician to be aware of the multiple factors that influence decisions of when and how to treat, and to proceed accordingly.

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