Corticosteroids for Multiple Sclerosis: II. Application for Disease-Modifying Effects

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Summary: Physicians who treat multiple sclerosis (MS) face the challenge of patients exhibiting ongoing disease activity, including exacerbations, loss of functional capabilities, intellectual decline, and radiologic progression, despite being on a disease-modifying agent (DMA). After searching for factors that might at least in part explain these changes—such as nonadherent drug-taking behavior, or the presence of interferon-neutralizing antibodies—some providers may ultimately decide to switch the patient to another DMA. In most circumstances, patients likely derive only partial effects from these agents, even in the absence of compromising factors. Thus, a number of factors must be considered in order to intensify the treatment regimen in response to disease progression. In the context of an inadequate treatment response to a DMA, some clinicians will convert the patient to an alternative therapy, and

others will instead use a second agent in combination with the first (the so-called platform agent). In the first of this two-part series, we explored the use of anti-inflammatory CS and ACTH to treat MS exacerbations. Although we underscored the limited availability of evidence-based studies to support specific regimens for this purpose, there is an even greater paucity of data to support the routine use of these agents in order to achieve chronic disease-modifying effects in those who continue to deteriorate clinically, radiographically, or both. Without doubt, a number of factors influence the formulation of combination treatment plan for MS. Nevertheless, we will focus on the rationale and practical schemes that can be considered for using corticosteroids (CS) (and perhaps even ACTH) in an attempt to modify various domains of ongoing disease activity. **Key Words:** Corticosteroids, ACTH, pulse steroids.

DISEASE PROGRESSION: A PRETEXT FOR USING CHRONIC CORTICOSTEROIDS?

In the management of individual patients, physicians continually reassess how successfully our therapies are controlling disease activity. Before rendering a declaration of unacceptable disease progression, which would provoke a change in the treatment regimen, a number of issues must be addressed.¹ We always ask patients about adherence to therapy and about any problems with adverse events that might compromise high fidelity use of therapy. Two elements are germane to understanding adherence: patients must take their medications correctly

(compliance) and with high fidelity over time (persistence).

It is important to carefully and systematically repeat the neurological examination, to identify the evolution of new signs that confirm the suspicion of disease progression. Similarly, patients should repeatedly have their functional abilities assessed (e.g., the execution of activities of daily living and work performance, as well as the observations of family members). This latter point is not trivial or to be overlooked. In fact, the patient often perceives meaningful and objective changes in neurological functioning, in advance of our ability to corroborate a change on the bedside office exam. It can truly be said that the real examination is in the shower, the bathroom, at the workplace, and wherever patients engage in recreational and family activities.

The performance of serial imaging studies to ascertain occult disease activity in a stable patient has not yet been systematically studied. Nonetheless, imaging is unequiv-

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ocally logical, appropriate, and a common standard of care, one that can help physicians make individual treatment decisions for their patients. In particular, during the relapsing–remitting (RR) phase of the MS disease course, which is characterized by inflammatory events (relapses, and the development of new brain and spinal cord lesions), it is critically important to liberally integrate magnetic resonance imaging (MRI) into the process of determining disease progression. This inflammatory phase of the disorder represents a time when we can in fact produce the greatest effect on the disease course with currently available agents. Some physicians routinely request MRIs (if they can get them paid for) on an annual basis. In more active patients, more frequent investigations may be required, perhaps every 3–6 months, to ascertain benefit from treatment interventions.

Once the physician has confirmed evidence of disease progression or breakthrough disease in a treatment-adherent patient, and without evidence of a drug-related neutralizing antibodies, it is appropriate to consider a variety of options for intensified treatment.^{2,3} Perhaps one of the most contentious issues in MS therapeutic decision-making concerns whether to switch to an alternative class of DMA, or instead to add a second agent to the first.

Switching is a good first option if we believe that the class of drugs used for certain forms of MS is not targeting the intended pathology of the disease for a given patient—a clinical judgment. For example, all the authors have managed patients on interferon (IFN) (low or high dose, and despite negative neutralizing antibodies) or on glatiramer acetate who just seem to continue exhibiting disease activity despite treatment and patient adherence to treatment regimen. In such a group—with what the clinician considers to be partial but not sufficient efficacy—combination therapy might be considered a good approach, seeking to achieve synergistic effects between the two drugs to better control disease activity.

Combination of drugs may lead to 1) antagonism, 2) balanced synergistic effect, or 3) inappropriate inhibition of inflammation, which in turn can decrease the theoretical possibility for repair: the concept of autoprotective immunity or neuroprotective immunomodulation. Despite the potential benefits of combination therapy (grounded in limited evidence-based medicine), the availability of superior efficacy in monotherapy natalizumab represents an important treatment consideration for those patients believed to be deriving insufficient efficacy from existing treatment.

The use of CS and ACTH (the latter remotely and more recently) has represented the mainstay of breakthrough treatment (whether for exacerbation or progression) in MS for quite some time. In practice, this approach is most often used for people who are developing

secondary–progressive disease or who have failed other therapies, and is sometimes used before intensive chemotherapeutic strategies such as mitoxantrone or cyclophosphamide. We now discuss the potential application of these agents for the purpose of achieving disease modification in those patients either exhibiting progression (clinical or radiographic) or who appear to be at high risk for future worsening, based on clinical, phenotypic, racial, or anatomic distribution or burden of disease.

JUSTIFICATION FOR CHRONIC PULSE CORTICOSTEROID THERAPY

There are few studies that have explored the effects of chronic steroid treatment in MS and its effect on relapses, disability or radiologic change in MS. A phase II study evaluated the effects of high-dose (500 mg) *versus* low-dose (10 mg) intravenous methylprednisolone (IVMP), administered every other month for 2 years in 108 secondary–progressive MS patients.⁴ The primary outcome was disability progression as measured on the Expanded Disability Status Scale (EDSS), and this showed no significant difference in the high-dose *versus* low-dose IVMP groups. The preplanned secondary analysis comparing time to the onset of sustained progression of disability reported a “relative treatment effect” in the high-dose regimen.⁴ The authors concluded that this observation provided sufficient clinical evidence to warrant a phase III efficacy trial comparing serial high-dose IVMP to low-dose IVMP in secondary–progressive patients.⁴

In a study involving relapsing–remitting MS (RRMS) patients, it was determined that serial treatment with pulsed IVMP appeared to be safe, and that it also served to prevent or delay whole brain atrophy and disability progression.⁵ Patients in the treatment group were assigned to receive pulsed IVMP for 5 days, followed by a 4-day oral taper (50 mg for 2 days followed by 25 mg for 2 days), every 4 months for 3 years and then every 6 months for an additional 2 years. The control group received no maintenance therapy of any type for their MS, but they were eligible to receive IVMP for relapses. MRI examinations were obtained at baseline and at study conclusion 5 years later.

There were no significant baseline MRI differences between the groups. Exit MRI evaluation revealed lesser T1-lesion volume (LV) development and diminished brain atrophy progression in the pulsed MP group (perhaps signifying a potential neuroprotective effect). The evolution of T2-LV, however, was similar in both groups. A post hoc analysis evaluated whether IVMP pulses affect the confluence and enlargement of T2 lesions in patients with RRMS.⁶ Calculations were performed for number, size, and LV of T2- and confluent T2-lesions. At study entry, the number, size and LV of

T2- and confluent T2-lesions were well matched in the two study arms. At the end of the study, patients who received IVMP pulses every 4–6 months for 5 years had significantly fewer confluent T2 lesions (105 vs 270, $P < 0.0001$), lower confluent T2-LV (5.4 vs 17.4 mL, $P < 0.00001$), and fewer large T2 lesions (>10 mm) (165 vs 541, $P < 0.00001$) than did patients who received IVMP only for relapses.

These findings suggest that treatment with pulses of IVMP may prevent the confluence of T2 lesions, which may in turn contribute to slower disability progression in the long term. It must be emphasized, however, that there is only a modest relationship between MRI measures at any given time and the corresponding level of disability (the so-called clinical–radiologic paradox). Notably, there was a 32.2% reduction ($P < 0.0001$) in the probability of sustained EDSS score worsening in the pulsed MP arm compared with the relapse treatment arm. At the end of the study, EDSS was better in the pulsed MP group (1.7 vs 3.4; $P < 0.0001$). Additional findings of note include, that out of 43 patients assigned to the pulsed MP group, only 2 dropped out due to toxic side effects; 2 others were lost to follow up. This suggests satisfactory tolerability and adherence with the pulsed CS regimen over the long term.⁵

Lack of adequate control of disease activity and DMA intolerance are the principal reasons that prompt the authors to recommend considering periodic CS pulses for our patients (TABLE 1). The disease course of MS and its related symptom constellations are quite heterogeneous. As such, it is crucial to individualize the approach to treatment in every case.

PRACTICAL ASPECTS OF UTILIZING CORTICOSTEROIDS FOR DISEASE MODIFICATION

Most clinicians with a substantial experience in the management of immune mediated disorders of any type including MS will frequently identify patients whom they consider to be good candidates for empiric CS therapy, to better control disease activity. Similarly, it is widely recognized that many such treated patients will report collateral benefits on quality of life, sense of well being, motor strength, spasticity, and fatigue. For instance, in a small retrospective study involving 10 patients, such benefits were reported in addition to a reduced number of acute exacerbations.⁷

ADDING CORTICOSTEROIDS TO STANDARD DISEASE-MODIFYING THERAPIES

Aside from the use of CS for exacerbations, these agents are sometimes combined with IFNs or glatiramer acetate. In one study, a synergistic effect on reducing

TABLE 1. Application of Corticosteroids for Disease Modification

Mechanism
Immunosuppressive
Immunomodulatory
Adhesion molecules or metalloproteinases
Evidence-Based Medicine
Some class II evidence for pulse steroid treatment controlling relapses and progression
Baseline Laboratory Examination
CBC with differentials; LFTs, BUN–Cr, electrolytes, glucose, lipid profile
Bone density,
Chest X-ray
Surveillance Laboratory Examination (6–12 months)
CBC with differentials; LFTs, BUN–Cr, electrolytes, glucose, lipid profile
Ophthalmologic examination (slit lamp, IOP)
Bone density
Dosing Instructions
1. Intravenous methylprednisolone: 1 g/day (1–5 days)-monthly/quarterly for maintenance
2. Oral prednisone: 500–1250 mg daily (1–5 days)-monthly, every other month, or quarterly for maintenance
3. Oral methylprednisolone: 1 g mixed in juice or smoothie taken orally with breakfast (1–5 days) monthly, every other month, or quarterly
4. Dexamethasone: 40–200 mg p.o./i.v. daily (1–5 days)-monthly, every other month, quarterly for maintenance
Safety Profile
GI side effects
Mania, insomnia, headache, anxiety
Hyperglycemia, diabetes, lipid derangements, bone loss, cataracts, skin changes, avascular necrosis, myopathy, cushingoid features, glaucoma

Abbreviations: BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; GI = gastrointestinal; IOP = intraocular pressure; LFTs = liver function tests.

MRI activity was confirmed when monthly IVMP treatment was added to weekly intramuscular IFN β -1a.⁸ Although we sometimes use IFNs or glatiramer acetate in combination with CS regimens (TABLE 1), to optimize chronic disease-modifying effects, we do not apply a similar approach to those patients being treated with natalizumab (Tysabri). Although we would consider using short courses of CS (up to 3 days with no taper) in natalizumab-treated patients who are experiencing moderate to severe exacerbations, the concern for severe immunosuppression, compromise in immune surveillance, and risk of PML strongly argues against using periodic pulses of CS with this agent.

A number of controlled trials have been completed or are underway to rigorously evaluate the safety and efficacy of this approach to treatment intensification. Results to date do not support a large treatment effect, if any. These studies are summarized as follows.

Glucocorticosteroid add-on therapy

Two recently published studies investigated the effect of glucocorticosteroids as add-on therapy to standard disease-modifying therapy in patients with MS. A randomized, double-blind, placebo-controlled pilot study of intravenous immunoglobulins (Ig) in combination with IVMP did not demonstrate the superiority of IVMP-IVIg in the treatment of moderate to severe acute relapses in MS.⁹ In another study, addition of prednisone therapy antagonized the beneficial effect of IFN β on up-regulation of IL-10 and soluble CD95.¹⁰ Both studies emphasized the complexity of using combination immunotherapies and the importance of evaluating their effects *in vivo* in well-controlled clinical trials.

Avonex Combination Therapy Study

The Avonex Combination Therapy (ACT) study¹¹ was a multicenter investigator-run safety and efficacy trial of IFN β -1a (Avonex) combined with methotrexate (MTX), intravenous methylprednisolone (IVMP), or both for RRMS patients with active disease on IFN β -1a monotherapy. Eligibility criteria included RRMS, EDSS score of 0–5.0, and active disease (≥ 1 relapse or gadolinium-enhancing MRI lesion) in the prior year on IFN β -1a therapy. Subjects were randomized to adjunctive weekly placebo or methotrexate (MTX) 20 mg p.o., each with or without IVMP 1000 mg/day for 3 days every other month, and followed for 12 months. Patients ($n = 313$) with similar baseline demographic, clinical and MRI characteristics were included.

The MTX-IVMP-IFN β -1a combinations were safe and well-tolerated. Analyses of ACT showed trends favoring the combination therapy regimens. New or enlarged T2 lesions, the primary outcome, averaged 1.53/patient overall, with upper-count category odds ratios (OR) in a main-effects proportional odds model for IFN β -1a-MTX of OR = 0.90 (95% confidence interval CI = 0.59–1.36) and for IFN β -1a-IVMP of OR = 0.74 (95% CI = 0.48–1.13). Relapses averaged 0.40/patient-year overall, with rate ratios (RR) in a main-effects negative binomial regression model for IFN β -1a-MTX of RR = 0.77 (95% CI = 0.51–1.16) and for IFN β -1a-IVMP of RR = 0.70 (95% CI = 0.46–1.05). Baseline to last observation T2 volume percent increase was reduced by IFN β -1a-IVMP ($P = 0.038$) but not significantly by IFN β -1a-MTX.

This study was stopped prematurely because of unacceptable low enrollment. Although there were favorable trends, combination therapy did not provide significant benefit when compared with monotherapy. Although the trial raises more questions than it answers, the information might suggest that, at least in some groups of patients, this regimen does not appear to provide significant benefits over single-agent therapy alone. In individual

patients, however, we cannot use the ACT Study results as a pretext to exclude this possibility.

Avonex–Azathioprine–Steroid Study

The Avonex–Azathioprine–Steroid (AAS) study¹² compared the efficacy of intramuscular IFN β -1a plus azathioprine (AZA) alone or in combination with prednisone, with that of intramuscular IFN β -1a monotherapy for patients with early RRMS. In this double-blind, placebo-controlled study, 181 patients were equally randomized into one of three treatment groups: 1) intramuscular IFN β -1a 30 μ g once weekly; 2) intramuscular IFN β -1a once weekly plus AZA 50 mg by mouth once daily; or 3) intramuscular IFN β -1a once weekly plus AZA by mouth once daily plus prednisone 10 mg by mouth every other day. The primary endpoint was annualized relapse rate (ARR) at 2 years. Patients were eligible for enrollment in a blinded 3-year study extension. At 2 years, the adjusted ARR was 1.05 for IFN β -1a, 0.91 for IFN β -1a plus AZA, and 0.73 for the triple combination, and the cumulative probability of sustained disability progression was 16.8% for IFN β -1a, 20.7% for IFN β -1a plus AZA, and 17.5% for the triple combination. There were no statistically significant differences among the groups for either measure at 2 and 5 years. All treatment groups had similar safety profiles, and combination therapy was well tolerated. This study demonstrated that at this time in IFN β -naïve patients with early active RRMS, combination treatment did not show superiority over IFN β -1a monotherapy.

Ongoing studies

The ASSERT study is investigating the effect of high-dose oral prednisone plus glatiramer acetate (Copaxone) *versus* glatiramer acetate alone on brain atrophy in RRMS patients.

Another ongoing study is investigating the effects of IFN β 1b (Betaseron) alone or in combination with bi-monthly IVMP in secondary–progressive MS patients will address the utility of CS to augment the efficacy of IFN therapy and to study the effect on the development of neutralizing antibodies.

Several studies in Europe are investigating the combination of pulse IVMP with subcutaneous IFN β -1a (Rebif) (22 and 44 mg).

DOSAGE, FREQUENCY, AND FORMULATION OF CORTICOSTEROIDS

High-dose CS (e.g., high-dose methylprednisolone, HDMP), is more commonly used in the treatment of acute MS exacerbations (see the part 1 companion article in this issue). They have been found to have statistically significant effects in improving pyramidal and cerebellar function in patients in an acute relapse, as well as in patients with progressive forms of MS.^{13,14} Furthermore,

the ONTT found that low-dose steroids (1 mg/kg/day $\times$ 14 days) was associated with twice the optic neuritis recurrence rate of the high-dose steroid or placebo groups.¹⁵ Although the mechanism underlying these differential clinical effects is not entirely characterized, we do know that HDMP exhibits an anti-inflammatory effect on cytokine cascades and produces a consistent attenuation of T cell activation. These agents also reduce the production and elaboration of several proinflammatory factors, such as nitric oxide and tumor necrosis factor.^{16,17} Further, CS exert effects on adhesion molecule interactions such that there is a reduction in mononuclear cell trafficking into the CNS, as reflected in the ability of CS to reduce gadolinium enhancements.¹⁸ Unfortunately, we have little data upon which to base specific serial treatment recommendations when using CS for the purpose of reducing future disease activity. Nevertheless, a number of options are available that are practical, well tolerated in most, and believed to be beneficial by both physicians and patients (TABLE 1).

CHRONIC CORTICOSTEROID ADMINISTRATION AND SAFETY

There are several safety concerns with steroids, whatever the formulation. Common electrolyte abnormalities such as hypernatremia and hypokalemia can be avoided with education and supplementation of nutrients and minerals. Insomnia is a frequent side effect, often requiring short-term medication. Although rare, particularly with pulse steroid applications, gastritis can occur with the oral or intravenous forms of CS. Some physicians pretreat with H₂ blockers or proton pump inhibitors concurrently with intravenous or oral formulations of steroids, whereas others add these agents only if gastritis or reflux occurs. Lower extremity edema is a potential problem, especially in the minimally mobile population. Judicious use of diuretics can be used along with judicious monitoring of electrolytes. Long-term improvement can also be achieved with lymphatic massage treatments and the use of compression hose. It is recommended that the patient receive treatment from a physical or occupational therapist who is certified in a form of lymphatic massage.

A potentially serious side effect of long-term corticosteroid therapy is steroid-induced osteoporosis.¹⁹ Epidemiological data indicate that the risk of fracture increases after 3 months of daily CS and that the risk of bone loss increases within 6 months of initiating therapy.^{20,21} Chronic use of steroids can lead to changes in bone mineral density and aseptic necrosis. Unlike long-term daily CS therapy, however, repeated intervals of pulse HDMP do not appear to promote osteoporosis or increase the risk of fracture. A study used dual-energy X-ray absorptiometry (DEXA) measurements of bone mineral density at the lumbar spine and femoral neck to compare

the effect of pulsed HDMP followed by oral prednisone administered over 8 years in 43 MS patients, who were compared with 61 healthy controls.⁵ Treatment with repeated HDMP 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.²² However, osteopenia, the precursor of osteoporosis, was observed more frequently in MS patients than in healthy controls.²² The study found that patients with MS had a 2.6-fold increased risk of developing osteopenia (defined as -1 to -2.5 SD from normal); However, osteopenia was found only in the control group, who had a significantly higher EDSS score than did patients in the IVMP group, suggesting that decreased mobility may contribute to bone loss more than corticosteroid use does. These data suggest that repeated pulses of HDMP over the long term may not result in substantially increased risk of osteoporosis in MS patients.

In our clinics, supplementation with vitamin D and calcium (500 mg, 2–3 times daily, as tolerated) and biannual DEXA scans are routinely recommended for patients receiving pulsed steroids. Screening for additional risk factors, including family history, tobacco use, diet and exercise, is also vital for prevention and treatment. Measurement of serum 25-hydroxyvitamin D levels followed by dose adjustment of vitamin D should also be considered. A serum level greater than at least 75–80 nmol/L is required to assure suppression of parathyroid hormone, which promotes resorption of calcium from bone.²³ In patients with evidence of osteopenia or osteoporosis, we use antiresorptive agents such as the bisphosphonates and calcitonin.

FUTURE DIRECTIONS

We fully recognize that rigorous class I studies are necessary for objectively clarifying the role of steroids for chronic disease-modifying effects in MS. Further, the conspicuous but subjective potential of these agents to exert beneficial effects on MS-related symptoms and quality of life should urgently be confirmed in controlled, masked clinical trials. Given the cost involved in such studies, and given that CS are generic agents without any patent protection, it will be formidable to achieve adequate funding in a timely manner for these very important areas of MS clinical research. Notwithstanding these obstacles, such studies are of great interest to patients, their families, and those of us who render care to the MS community.

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