Acute Multiple Sclerosis Relapse

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ABSTRACT

Purpose of Review: This article discusses acute exacerbations (relapses) of multiple sclerosis (MS). Relapses are a hallmark of MS and are often associated with significant functional impairment and decreased quality of life. This review discusses the proposed pathophysiology of MS relapses, triggering factors, associated markers, variants of clinical presentation, and diagnostic recommendations.

Recent Findings: Most MS exacerbations are followed by a period of repair leading to clinical remission; however, residual deficits may persist after MS relapse and contribute to the stepwise progression of disability. Treatment of MS relapses is important as it helps to shorten the duration of disability associated with their course. Successful treatment of relapse helps patients with MS obtain a vital sense of being able to gain control over the disease. Patients with relapsing MS who receive treatment report better outcomes than those who are simply observed. This article discusses treatment options for MS relapse, including systemic corticosteroids, adrenocorticotropic hormone, and plasma exchange. Recent findings related to the mechanisms of action of steroids and adrenocorticotropic hormone are also reviewed, and other potential therapies are assessed. A proposed algorithm for MS relapse management is presented, including strategies for steroid-resistant MS exacerbations.

Summary: MS relapses need to be recognized in a timely manner and treated using recommended therapeutic methods.

Continuum (Minneap Minn) 2016;22(3):799–814.

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Relationship Disclosure: Dr Berkovich has served on the advisory boards of Bayer AG, Biogen, Mallinckrodt Pharmaceuticals, Novartis AG, Sanofi Genzyme, and Teva Pharmaceutical Industries Ltd, and as a consultant for Acorda Therapeutics; Avanir Pharmaceuticals, Inc; Biogen; Sanofi Genzyme; and Teva Pharmaceutical Industries Ltd. Dr Berkovich has received personal compensation for speaking engagements from Acorda Therapeutics; Avanir Pharmaceuticals, Inc; Biogen; Novartis AG; Sanofi Genzyme; and Teva Pharmaceutical Industries Ltd.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Berkovich reports no disclosure.

INTRODUCTION

The majority of patients with multiple sclerosis (MS) have relapsing (or, following the new descriptive classification, active)[1] types of the disease. MS relapses are typically defined as new or worsening neurologic deficits lasting 24 hours or more in the absence of fever or infection. Similar symptoms occurring in the presence of fever, heat exposure, or infection are commonly called *pseudoexacerbations*.

Relapses are a hallmark of MS.[2] Jean-Martin Charcot's original definition of a clinical MS relapse was focal disturbance of function affecting a white matter tract that lasts for more than 24 hours, does not have an alternative explanation, and is preceded by more than 30 days of clinical stability.[3] The criteria for relapse in recent clinical trials include a minimum of 24 to 48 hours of symptom duration and changes in functional measures assessed by disability and functional scores; these criteria, although intended to provide objective assessment to support the diagnosis of an MS relapse, may not be very helpful in actual practice. High clinical significance, reflected in the most common primary outcome in contemporary clinical trials in MS (relapse rate), suggests the need to study relapses to know whether acute disease activity (relapses) may impact

KEY POINTS

- Relapses are a hallmark of multiple sclerosis. Jean-Martin Charcot's original definition of clinical multiple sclerosis relapse was focal disturbance of function affecting a white matter tract that lasts for more than 24 hours, does not have an alternative explanation, and is preceded by more than 30 days of clinical stability.
- From a patient's perspective, a multiple sclerosis relapse is associated with a significant increase in economic costs as well as a decline in health-related quality of life and functional ability.
- Multiple sclerosis relapses may reflect the formation of new demyelinating activity or reactivation of previously existing demyelinating lesions located in any segment of the central nervous system.
- It is important to rule out conditions that may lead to pseudoexacerbations, including fever, infections (most commonly urinary tract and upper respiratory infections), stress, and heat exposure.

disease progression and whether the value of adequately treated relapse may expand beyond quality-of-life improvement and symptom management.

From a patient's perspective, an MS relapse is associated with a significant increase in economic costs as well as a decline in health-related quality of life and functional ability.[4] For the vast majority of patients with MS, relapses are one of the biggest concerns associated with the disease, and the unpredictability of MS exacerbations complicates the potential impact on quality of life.[5]

PROVOKING FACTORS AND CLINICAL PRESENTATIONS OF MULTIPLE SCLEROSIS RELAPSES

MS relapses may reflect the formation of new demyelinating activity or reactivation of previously existing demyelinating lesions located in any segment of the central nervous system (CNS).[6,7] Commonly seen symptom complexes are related to acute inflammatory processes involving the optic nerve, spinal cord, cerebellum, or cerebrum. Thus, presenting symptoms may vary or may be a combination of visual disturbances, motor and sensory impairments, coordination and balance issues, and cognitive deficits.[6,7]

Cognitive and psychiatric presentations of MS relapses have recently received much-deserved attention, as these may occur in the absence of classically expected neurologic symptoms.[8] So-called isolated cognitive relapses, which may not be associated with subjective cognitive deficits or depression, were found to be accompanied by significantly reduced objective cognitive performance.

It is important to rule out conditions that may lead to pseudoexacerbations, including fever, infections (most commonly urinary tract and upper respiratory infections), stress, and heat exposure.[5] However, while infections frequently mimic relapses and are the common cause of pseudoexacerbations, the global role of infections and pathogens in MS activity may not be as straightforward. Pathogens that have been hypothesized to predispose patients to the initial development of MS include bacteria (such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Staphylococcus*) and viruses (such as Epstein-Barr virus and human herpesvirus 6). In contrast, infection with certain parasites, such as helminths, appears to protect against the development or exacerbation of MS.[9] Thus, complex interfaces between the CNS, various infectious pathogens, and the immune responses they provoke need to be further explored. In clinical practice, distinguishing between a pseudoexacerbation brought on by a bacterial infection, such as a urinary tract infection, and a true MS relapse warranting treatment remains a key clinical challenge.

Different neurobiological scenarios related to different pharmacotherapy phases may potentially predispose patients to MS relapse, including the first weeks or even months after disease-modifying therapy initiation when the desired immunomodulated stage has not been yet achieved. The discontinuation of a previously effective disease-modifying therapy may also predispose patients to MS relapse; this has most commonly been associated with discontinuation of natalizumab.[10] Tumor necrosis factor (TNF)–blocking drugs (eg, infliximab, etanercept) given for comorbid conditions have been shown to promote the onset or exacerbation of MS.[11] Furthermore, since reproductive hormones have an important role in regulating immune responses, it

should be noted that certain assisted reproductive technologies (in particular, the use of a gonadotropin-releasing hormone [GnRH] agonist) may significantly increase the risk of MS exacerbation in patients receiving them.[12] Awareness of the specifics of the immunomodulatory background and a patient's hormonal milieu is important for apt recognition of and approach to an MS relapse.

Studies that relate stress to the risk of developing MS have found discordant results; however, research evaluating the association of stress with MS exacerbation shows a fairly consistent direct correlation. Higher stress levels also appear to increase the risk of the development of gadolinium-enhancing lesions. In patients with MS, perceived stress and mood disturbances seem to correlate with induced production of interleukin (IL) 6 and IL-10; in addition, compared to controls, subjects with MS exhibited a significant fourfold increase in the production of IL-12.[13] Stress management therapy and cognitive-behavioral therapy may prove effective in reducing stress-related MS exacerbations.[14]

It has been noted that seasonal variation of relapse rate and relapse onset follows an annual cyclical sinusoidal pattern with zenith in early spring and nadir in autumn in both hemispheres. The MSBase Study Group found that whereas visual, brainstem, and sensory relapses occurred more frequently in early disease, pyramidal, sphincter, and cerebellar relapses were more common in older patients and in more progressive courses. Female patients presented more frequently with sensory or visual symptoms; men were more prone to pyramidal, brainstem, and cerebellar relapses. Relapse phenotype was predicted by the phenotypes of previous relapses. Sensory, visual, and brainstem relapses showed better recovery than other relapse phenotypes.[15] It is worth mentioning that, according to some observations,[16] isolated cognitive relapses seem to be relatively rare; in the setting of possible cognitive relapse, it is exceedingly important to rule out subjective changes associated with exposure to emotional or physical stress, insomnia, and medication side effects. Implementing a simple screening tool, such as the Montreal Cognitive Assessment (MoCA) (*www.mocatest.org*), may prove helpful in objectivizing the symptoms (provided that baseline evaluation is available).

PROPOSED IMMUNOBIOLOGY OF MULTIPLE SCLEROSIS RELAPSES

Acute inflammatory events are the mechanism by which demyelination and axonal loss are believed to occur.[17] The activation of the immune process is initiated systemically, resulting in migration of activated immune cells into the CNS, where they are reactivated and result in parenchymal inflammation. The acute inflammation in MS may be focal, multifocal, or diffuse and is characterized by infiltration of activated lymphocytes, macrophages, and microglia, with involvement of cortex, white matter, and deep gray matter with myelin destruction; axonal, neuronal, and synaptic loss; astroglial reaction; remyelination; and synaptic rearrangement.[17,18] Deregulated immune response, including inflammatory cells (T cells, B cells, and macrophages) and mediators (cytokines, chemokines, matrix metalloproteinases, and complement), contributes to the expansion of autoreactive T cells; proinflammatory shifts promote increased blood-brain barrier permeability along with lymphocyte and monocyte extravasation.[19]

KEY POINT

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KEY POINTS

- Residual deficits may persist after multiple sclerosis relapse and contribute to the stepwise progression of disability. Treatment of multiple sclerosis relapses is important as it helps to shorten relapses and lessen the disability associated with their course.
- The era of pharmacologic treatment of multiple sclerosis started with adrenocorticotropic hormone.

A quantitative relationship between treatment effects on MRI lesions and clinical relapses has been shown.[20] The effect of treatment on MRI lesions over 6- to 9-month follow-up periods predicted the effect on relapses over 12- to 24-month periods with 95% accuracy in eight of nine trials.[20] According to classic works by Bruce Trapp,[21,22] the number of transected axons increases with the level of activity in MS lesions; there can be more than 11,000 transected axons in active MS lesions. The question many clinicians may ask is how do we effectively translate this information to the level of every individual patient? For example, should new gadolinium-enhancing lesions be recognized as a surrogate marker for an active MS process? Most experts would agree with this. If so, can it be seen as a radiologic marker of MS relapse? This clearly has been the theory in enrollment strategies of clinical trials. If new gadolinium-enhancing lesions are indicative of acute MS inflammation, should we treat patients who have MS with enhancing lesions as we would treat patients with MS relapse? Some experts would say yes,[17] but no consensus exists with respect to this dilemma at present, in part because it is difficult to evaluate the immediate or delayed benefits of treating acute lesions that do not have a clinical correlate.

MULTIPLE SCLEROSIS TREATMENT: RESEARCH AND PRACTICE

Most MS exacerbations are followed by a period of repair leading to clinical remission and sometimes, especially early in the disease course, to a complete recovery; however, residual deficits may persist after MS relapse and contribute to the stepwise progression of disability.[2] Treatment of MS relapses is important as it helps to shorten the duration of disability associated with their course. Successful treatment of relapse also has an important psychological aspect: it helps patients with MS obtain a vital sense of being able to gain control over the disease.[5] Not surprisingly, patients who receive treatment for MS exacerbations report better outcomes than those who are simply observed.[23]

Bed rest was the only treatment of choice for MS relapse in the early 20th century; it was accepted as a useful measure to help recovery and shorten the duration of attack.[5] The era of pharmacologic treatment of MS started with adrenocorticotropic hormone (ACTH), which was the first compound successfully studied and approved for relapse treatment. Arguably the very first controlled clinical trial in MS studied 40 patients with acute exacerbations who were treated with either ACTH or saline. The study ''confirmed the clinical impression that the hormone exercises a favorable effect on the outcome of some of such episodes.''[24]

Results of a much larger and well-designed controlled double-blind multicenter study were published by Rose and colleagues.[25] A total of 197 patients were enrolled from 10 centers throughout the United States and randomly assigned to either 40 units of ACTH gel or placebo gel IM 2 times a day for 7 days, then 20 units 2 times a day for 4 days, and 20 units once a day for 3 days. Reported beneficial effects led to acceptance of ACTH gel as a treatment for MS relapse and eventually to US Food and Drug Administration (FDA) approval of ACTH gel for this indication in 1978.

It is worth mentioning that, at that time, the mechanism of action of ACTH was attributed exclusively to its steroidogenic potential.[5] However, more recent data in other disease

states, such as nephrotic syndrome, opsoclonus-myoclonus, and infantile spasms, suggest that steroidogenic action alone cannot explain the efficacy of ACTH in these conditions, since corticosteroid treatment has suboptimal efficacy in them. Recently, it has been shown that ACTH has direct anti-inflammatory and immunomodulatory effects via activation of central and peripheral melanocortin receptors, in addition to the effects achieved by systems originating in the adrenal gland.[26] ACTH is a strong melanocortin agonist; it binds to all five known classes of melanocortin receptors, of which only one, melanocortin 2 receptor, is implicated in adrenal steroidogenesis. Melanocortin 1 receptor is expressed in melanocytes, epithelial cells, monocytes, neutrophils, lymphocytes, podocytes, periaqueductal gray matter in the CNS, microvascular endothelial cells, astrocytes, and Schwann cells. Melanocortin 2 receptor is the receptor in the adrenal glands underlying the steroidogenic actions of ACTH and has also been localized to osteoblasts and skin. Melanocortin 3 receptor and melanocortin 4 receptor have been identified in the CNS; melanocortin 3 receptor occurs primarily in the hypothalamus and limbic system, while melanocortin 4 receptor is the prevalent receptor in the CNS, with wide expression in the cortex, thalamus, hypothalamus, brainstem, spinal cord, and astrocytes. Melanocortin 5 receptor is widely distributed and occurs in exocrine glands and lymphocytes. Recently, it was found that ACTH stimulates proliferation of oligodendrocyte progenitor cells and provides benefit by increasing the number of oligodendrocyte progenitor cells, accelerating their development into mature oligodendrocytes and reducing oligodendrocyte progenitor cell death from toxic insults.[26]

The presumption that the efficacy of ACTH results solely from its corticotropic effects may not be accurate, but back in the 1970s and 1980s, it led to increased interest in high-dose corticosteroids for the treatment of MS exacerbations. Since that time, the focus has shifted to systemic steroids as the preferred treatment option for MS relapse.

The second medication, and at this point the only medication other than ACTH approved by the FDA for MS relapse treatment, is IV methylprednisolone.[27] Readily available, inexpensive, and robust, today's systemic steroids are the first line of MS relapse treatment and clearly are the most commonly used treatment for this indication.

Initially, the mechanism of action of systemic corticosteroids in the treatment of acute relapse was attributed to the immunologic alterations they cause, and it was believed "likely that the main, if not the sole, mechanism is the resolution of edema."[28] Today, the main mechanism of glucocorticoid action is attributed to induction of T-cell apoptosis, leading to reduced lymphocyte infiltration into the CNS with decreased overall proportion of T-regulatory cells and increased proportions of CD39-expressing T-regulatory cells and monocytes.[17]

Several studies have compared IV methylprednisolone to ACTH and to placebo.[5] Interestingly, the comparison trials have repeatedly failed to demonstrate significant differences in efficacy between the systemic steroids and ACTH, although different protocols were used. For example, in the double-blind randomized controlled study by Thompson and colleagues,[28] relative efficacy of IV methylprednisolone and ACTH for MS relapse was evaluated. A total of 61 patients were randomly assigned to either IV

KEY POINTS

- Recently, it has been shown that adrenocorticotropic hormone has direct anti-inflammatory and immunomodulatory effects via activation of central and peripheral melanocortin receptors, in addition to the effects achieved by systems originating in the adrenal gland.
- Adrenocorticotropic hormone is a strong melanocortin agonist; it binds to all five known classes of melanocortin receptor, of which only one, melanocortin 2 receptor, is implicated in adrenal steroidogenesis.
- Readily available, inexpensive, and robust, today's systemic steroids are the first line of multiple sclerosis relapse treatment and clearly are the most commonly used treatment for this indication.

methylprednisolone (1 g/d for 3 days) plus IM placebo injections (daily for 14 days) or IV placebo (daily for 3 days) plus IM ACTH (for 14 days: 80 units/d for 7 days, 40 units/d for 4 days, and 20 units/d for 3 days). ''A clear improvement was observed in both groups,'' but ''no significant difference between the 2 groups in either rate of recovery or final outcome at 3 months'' was found. Still, it was noted that the ''3-day course of IV treatments rather than 14 days of IM injections has obvious advantages,'' such as a shorter duration of treatment.

The Optic Neuritis Treatment Trial compared oral prednisone (1 mg/kg/d for 14 days; n = 156), IV methylprednisolone (1 g/d for 3 days followed by oral prednisone 1 mg/kg/d for 11 days; n = 151), and oral placebo (n = 150) for 14 days in the treatment of 457 patients with optic neuritis. It was found that visual function recovered faster in the group receiving IV methylprednisolone than in the placebo group; although the differences between the groups decreased with time, at 6 months, the IV methylprednisolone group had better visual fields, contrast sensitivity, and color vision, although not better visual acuity. The outcome in the oral prednisone group did not differ from that in the placebo group, and, disturbingly, the rate of new episodes of optic neuritis was higher in the oral prednisone group than in the placebo group, but not in the IV methylprednisolone group. It was concluded that IV methylprednisolone speeds the recovery of visual loss due to optic neuritis, but oral prednisone alone is an ineffective treatment and increases the risk of new episodes of optic neuritis.[5]

The dosages of IV methylprednisolone used in MS relapse studies have differed considerably, ranging from as low as 40 mg/d to 500 mg/d up to 15 mg/kg/d IV (which is close to 900 mg/d to 1200 mg/d) to 1g/d.[5] The low dosages were found to be ineffective, and dosages from 500 mg/d to 1 g/d became a widely accepted and preferred regimen. The length of treatment also varied in the studies, and the general consensus on how long an MS relapse should be treated has undergone a notable change over the years. While back in the 1960s to the 1980s it was a common practice to treat an MS exacerbation with ACTH for 4 to 5 weeks, more recently, significantly shorter courses of 3 to 7 days of IV methylprednisolone have been found to be quite adequate.[5]

Since the 1990s, high-dose oral methylprednisolone has been studied, which in most trials was found to be comparable to the effects of IV methylprednisolone.[5] Financial and other practical advantages associated with the oral route of administration are apparent.[6] The Cochrane Database of Systematic Reviews analyzed five different studies and concluded that oral versus IV administration of methylprednisolone does not demonstrate any significant differences in clinical, imaging, and pharmacologic outcomes.[29] The 2015 oral versus IV steroid study by Le Page and colleagues[30] supported this as well.

Adverse Events During Steroid and Adrenocorticotropic Hormone Therapy

Susceptibility to steroid- or ACTH-induced adverse effects and their relative frequencies vary from patient to patient and depend on several factors, including the individual patient's comorbidities and the dose, duration, and possibly type and route of administration.[7] In randomized clinical trials, serious side effects were rare with short-term use of either steroids or ACTH.[5]

The most frequently reported corticosteroid side effects in short-term use for MS exacerbations are gastrointestinal symptoms, weight gain, edema, mood changes, dysphoria, anxiety, insomnia, musculoskeletal pain, palpitations, edema, acne, weight gain, headache, and unpleasant (metallic) taste. Less frequently reported are hyperglycemia, hypertension, moon face, hirsutism, and unusual taste during or after IV infusion.[5] Among adverse events involving the musculoskeletal system, osteoporosis has been estimated to develop, in general, in at least 50% of individuals requiring long-term corticosteroid therapy; however, short-term steroid treatment for relapse does not seem to reduce bone density in fully ambulatory patients with MS.[5] Severe psychiatric disorders, such as psychosis, depression, or manic episodes, are reported in up to one-third of patients treated with steroids; the risk of psychosis appears to be highest at the start of therapy and may be higher in women. Insomnia has been reported by about 50% of all patients on corticosteroid treatment. Other frequently reported side effects are infections, the most common of which are pneumonia, septic arthritis/bursitis, and complicated urinary tract infections.[5–7] The effects of steroid treatment on carbohydrate metabolism appear to be proportional to the patient's preexisting status. Aseptic (avascular) necrosis of the hip has been reported to be a potential complication of systemic steroid use, and its development is unpredictable; it may occur within the first few weeks of therapy.[5–7]

Steroid resistance is a known problem frequently reported in the setting of relapse treatment; this phenomenon was linked to downregulation of glucocorticoid receptor expression. According to the patient-reported outcomes from the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry, 32% of patients treated with IV methylprednisolone and 34% of patients treated with an oral corticosteroid indicated their symptoms were worse 1 month after treatment than prerelapse. (For comparison, worsening was reported by 39% of untreated [observation-only] patients 1 month after the relapse started.) Of patients treated with IV methylprednisolone, 30% indicated their treatment made relapse symptoms worse or had no effect, as did 38% of patients treated with an oral corticosteroid. (For comparison, 76% of observation-only [untreated] patients reported similar outcomes 1 month after relapse started.[23])

Nevertheless, corticosteroids may act in unpredictable ways in the context of autoimmune conditions, and it is difficult to foresee when patients will respond favorably to corticosteroids, both in terms of therapeutic response and tolerability profile.[31] Disturbingly, a study of the effect of corticosteroids on the expression of cellular and molecular markers of spontaneous endogenous remyelination in the toxic nonimmune cuprizone animal model at early and intermediate remyelination, as well as steroidal effects in primary astrocyte and oligodendrocyte progenitor cultures, has shown that in addition to the well-known beneficial effects on inflammatory processes, the steroids have a negative impact on remyelination.[32]

Concomitant medications should be given with IV methylprednisolone to mitigate side effects (eg, ranitidine for gastrointestinal prophylaxis, diphenhydramine or other sleep aid for insomnia). Additional monitoring may be necessary, especially for patients

KEY POINT

- More data are needed before firm recommendations can be made to support the use of adrenocorticotropic hormone versus IV methylprednisolone or oral steroids, especially considering the high price of adrenocorticotropic hormone gel. Thus, at this point, the use of adrenocorticotropic hormone should be restricted to cases of steroid intolerability or suboptimal response to corticosteroids.

with comorbid conditions such as diabetes mellitus or hypertension. In general, a low-salt, low-carbohydrate diet is recommended. To minimize transient weight gain and acne, potassium supplementation may be either prescribed or added through dietary choices such as dried apricots.

Patients should be advised to expect a response to the treatment within 2 to 3 weeks. Adequate efficacy at reducing relapse symptoms means return to the patient's previous level of functioning. When approaching the patient with an MS relapse, certain circumstances warrant hospitalization, such as acute gait failure requiring inpatient rehabilitation, lower brainstem symptoms with aspiration risk, or comorbid diabetes mellitus or poorly controlled hypertension necessitating close monitoring of serum glucose and blood pressure, respectively.

With ACTH, adverse effects are thought to be related primarily to its steroidogenic effects and are similar to the adverse effects of corticosteroids, although according to clinical observations (and in concord with a significantly smaller amount of triggered inner steroid cortisol production in comparison to the dosage of exogenous methylprednisolone), some side effects seem to be milder compared to systemic steroids. Susceptibility to new infection and risk of reactivation of latent infections may be increased, and adrenal insufficiency may occur after abrupt withdrawal of the drug following prolonged therapy. Cushing syndrome, elevated blood pressure, salt and water retention, and hypokalemia may be seen, and masking of symptoms of other underlying diseases or disorders may occur. A risk of gastrointestinal disturbances exists in patients with certain gastrointestinal disorders; acne and, rarely, psychiatric symptoms may be observed.[5]

Trends

Undoubtedly, given the issues of tolerability and efficacy, options other than systemic steroids are needed for MS relapse treatment; this is one of the reasons for the renewed focus on ACTH. Another reason for the focus on ACTH is the increasing body of knowledge on ACTH mechanisms and its direct anti-inflammatory and immunomodulatory effects via activation of central and peripheral melanocortin receptors, in addition to its well-known steroidogenic effects.[5,26]

Although data from clinical trials have not demonstrated a difference in the efficacy of ACTH and corticosteroids, anecdotal reports exist of patients who do not respond to steroids but respond to ACTH. Likewise, some patients who cannot tolerate steroids may tolerate ACTH.[5] Still, more data are needed before firm recommendations can be made to support the use of ACTH versus IV methylprednisolone or oral steroids, especially considering the high price of ACTH gel. A single course of ACTH gel was widely reported in 2012 to cost $28,000, significantly more expensive than a course of methylprednisolone for the treatment of MS relapse. In light of this, particularly in an era in which more scrutiny is being directed to drug pricing and overall fiscal responsibility in health care, the use of ACTH should be restricted to cases of significant steroid intolerability or suboptimal response to corticosteroids.

Potential differences in the safety of ACTH relative to corticosteroids is an important unanswered question. For example, the risk of bone loss is particularly important in the context of high-dose or extended use of corticosteroids, leading to excessive osteoclastic bone removal and osteonecrosis via increased apoptosis of osteoblasts. In contrast, potential osteoprotective

properties of ACTH were shown in experimental studies.[26] If supported by well-designed clinical trials, the data may prove to be practical in the setting of comorbid osteoporosis; at this point, however, the existing data favoring ACTH for reduced risk of bone loss are purely experimental, and further clinical studies are necessary. Thus, despite the growing volume of preclinical data currently available on ACTH and melanocortins, many clinical questions remain to be answered.

Second-line Treatments

Data on the prevalence of treatment-resistant MS relapses (not responding to either corticosteroids or ACTH) vary; according to the NARCOMS registry, steroid-refractory exacerbations may be observed in up to half of patients with MS. Clinicians should identify such treatment failures by reassessing the patient's status 2 to 3 weeks after the treatment; one possible way to do this is to encourage the patient to call the clinic 2 to 3 weeks after the treatment and report the current status or lack of treatment response. Optimal treatment response means complete return to the prerelapse level of functioning; lack of complete recovery constitutes suboptimal response. Mild lingering symptoms, such as sensory changes not interfering with daily activities, usually do not need additional treatment. However, major relapse residua, such as severe persistent visual impairment and balance and motor deficits, may, on an individual basis, warrant consideration of expeditious use of a second-line relapse therapy.

Several treatment alternatives, including plasma exchange,[33–38] cyclophosphamide,[39] intravenous immunoglobulin (IVIg),[40–43] and natalizumab,[44] have been studied; at this point, plasma exchange is the only second-line option supported by strong clinical evidence.

As previously discussed, B-cell and humoral antibody-driven mechanisms have an important role in MS exacerbation. The 2011 American Academy of Neurology guideline recommends plasma exchange as a secondary treatment for severe flares in relapsing MS.[36] In a large multicenter randomized double-blind controlled trial, an 8-week course of 11 plasma exchange treatments for MS relapse treatment was studied.[33] A total of 116 subjects were randomly assigned to either sham or true plasma exchange, and both groups received identical treatment with IM ACTH and oral cyclophosphamide. Plasma exchange produced significant reductions in IgG, IgA, IgM, C3, and fibrinogen in serum. The results suggested that plasma exchange given with ACTH plus cyclophosphamide enhances recovery from an exacerbation of disease in patients with relapsing-remitting MS. Results of another randomized double-blind sham-controlled study of either plasma exchange or sham treatment in patients who did not respond to IV methylprednisolone showed significant efficacy of plasma exchange in this category of patients not responding to the steroids. In the study, 12 subjects with MS and 10 with other acute inflammatory demyelinating conditions were randomly assigned to either plasma exchange or sham treatment, which was given as seven exchanges every other day for 14 days. Nineteen courses of plasma exchange were performed, resulting in eight moderate or marked improvements; only one moderate improvement was noted across 17 courses of sham treatment.[34] In a subsequent retrospective review of 59 steroid-unresponsive demyelinating

KEY POINTS

- If multiple sclerosis relapse is confirmed, treatment should be started as soon as possible. For first-line treatment, IV methylprednisolone 1 g/d for 3 to 5 days is generally recommended. The need for oral prednisone taper following IV methylprednisolone should be considered on an individual basis.
- Although not US Food and Drug Administration approved for this indication, oral administration of high-dose methylprednisolone instead of IV methylprednisolone may be suggested (especially for patients with excellent response to steroids but poor venous access).

events treated by plasma exchange, Keegan and colleagues[35] found that male gender, preserved or brisk reflexes, and early initiation of treatment (within less than 60 days) were associated with improvement. Furthermore, responsiveness to plasma exchange was correlated with the pathologic features of demyelination; subjects who responded to plasma exchange in this series had a particular pattern of demyelination characterized by the presence of antibodies and complement, whereas nonresponders had pathologic characteristics of T-cell/macrophage-associated demyelination or distal oligodendrogliopathy. In a 2013 observational study of plasma exchange for steroid-refractory relapses, 93.3% of patients showed a marked to moderate clinical improvement, and 46.7% recovered their baseline Expanded Disability Status Scale (EDSS) score 3 months post–plasma exchange. On the post–plasma exchange MRI, 60% showed radiologic resolution, 20% had partial resolution, and 20% had no resolution.[37]

The role of IVIg in MS relapse treatment remains to be defined. While many anecdotal observations of beneficial effects of IVIg in the treatment of MS relapses exist, most published clinical studies provide no clear evidence to support this. Results of a large double-blind placebo-controlled trial by Noseworthy and colleagues[39] suggested that delayed IVIg administration had no effect on recovery from optic neuritis. Part of the controversy results from the fact that IVIg is usually tried after IV methylprednisolone administration; thus, possible delayed effects of IV methylprednisolone may overlap and obscure the pure IVIg effects. The role of IVIg as a possible therapeutic option for treating MS relapse will require further study.

PRACTICAL RECOMMENDATIONS

It is generally accepted that while mild MS exacerbations may not require immediate treatment, moderate to severe relapses with disabling symptoms should be treated using a first-line treatment.[5] In general, starting treatment as early as possible (within 1 week of MS relapse symptom onset) is considered best. It has been observed that relapse treatment can be successfully initiated as late as 1 to 2 months into a relapse.[6]

The author proposes the following algorithm developed on generally accepted principles (**Figure 6-1**):

- Evaluate patients with possible MS relapse within 1 week (or 5 working days) of the onset of new or worsened symptoms; rule out pseudoexacerbation (clinical and laboratory signs of infection, history of exposure to temperature extremes). MRIs are not indicated for MS relapse diagnostic purposes as MS exacerbation is a clinical diagnosis; however, an MRI may be done for a different reason, such as to assess adequacy of the current disease-modifying therapy.
- If MS relapse is confirmed, start treatment as soon as possible:
  - For first-line treatment, IV methylprednisolone 1 g/d for 3 to 5 days is generally recommended.
  - The need for oral prednisone taper following IV methylprednisolone should be considered on an individual basis (such as individual preference of patient or provider), although some data suggest no additional benefit for oral taper.[45]
  - Although not FDA approved for this indication, oral administration of high-dose methylprednisolone

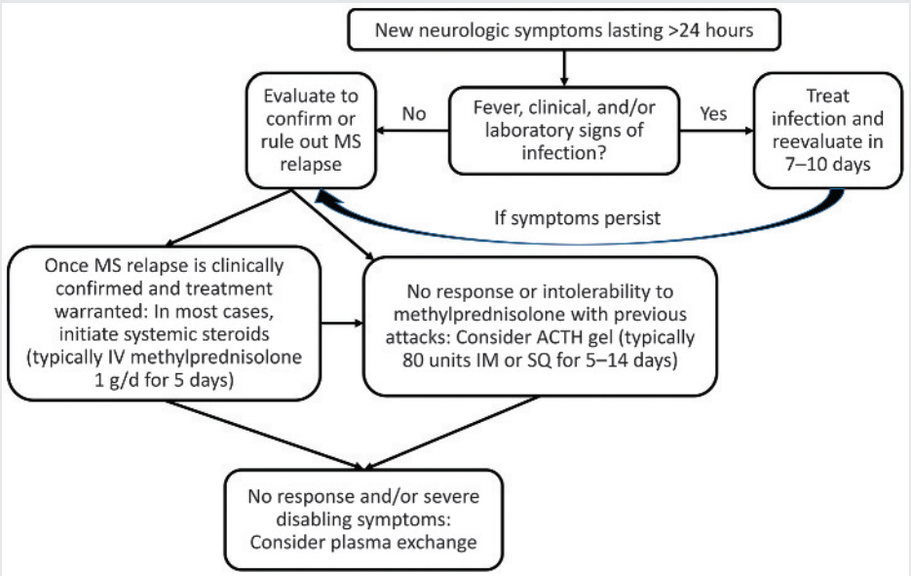

FIGURE 6-1 Proposed algorithm for multiple sclerosis relapse management.

ACTH = adrenocorticotropic hormone; IM = intramuscular; IV = intravenous; MS = multiple sclerosis; SQ = subcutaneous.

instead of IV methylprednisolone may be suggested (especially for patients with excellent response to steroids but poor venous access).[6]

- Patients who previously could not tolerate systemic steroids, or those who did not improve or had significant side effects with methylprednisolone, may be offered another FDA-approved option: ACTH. It should be noted that effects of IV methylprednisolone or oral high-dose methylprednisolone may be delayed; therefore, as a general rule in the author's practice, we wait 2 to 3 weeks after the last dose of high-dose corticosteroids before initiating ACTH gel therapy administered either IM or subcutaneously at a dose of 80 units/d for at least 5 days and up to 15 days.[5] Our clinic's experience indicates that the majority of patients with MS in acute exacerbation for whom methylprednisolone treatment failed or could not be tolerated experience positive clinical outcomes and fewer adverse events with ACTH gel treatment (**Case 6-1**).[5]
- For patients with disabling MS relapse symptoms that do not respond to initial treatment, especially patients who experience clinical worsening of symptoms following first-line treatment, plasma exchange should be considered on an individual basis. Plasma exchange should be administered every other day for up to 5 to 10 exchanges. A decision on the need for prolonged treatment, up to 10 sessions, can be made based on suboptimal response following the initial five sessions (**Case 6-2**).
- Patients who develop new neurologic symptoms after a recently treated relapse need to be evaluated to rule out possible pseudoexacerbation (**Case 6-3**).

KEY POINTS

- Patients who previously could not tolerate systemic steroids, or those who did not improve or had significant side effects with methylprednisolone, may be offered another US Food and Drug Administration–approved option: adrenocorticotropic hormone.
- For patients with disabling multiple sclerosis relapse symptoms that do not respond to initial treatment, especially patients who experience clinical worsening of symptoms following first-line treatment, plasma exchange should be considered on an individual basis.

Case 6-1

A 43-year-old woman with relapsing-remitting multiple sclerosis (MS) called the office with a report of new sensory changes and stiffness of her lower extremities associated with frequent urination and new urinary retention. She reported no fever. The symptoms started 2 days prior to presentation and were not getting better.

She was diagnosed with MS 3 years previously after an initial episode of diplopia and an MRI evaluation revealing several brain, brainstem, and thoracic cord lesions. At that time, she was treated with 1 g IV methylprednisolone for 3 days, which was effective but was associated with a significant psychotic reaction and strong suicidal ideation. Disease-modifying therapy was initiated thereafter (glatiramer acetate 20 mg/d subcutaneously), which was well tolerated. Initially, she had good compliance but admitted to ''skipping injections here and there'' over the past 7 months because of injection site reactions and ''running out of sites.'' Her most recent MRIs were performed 9 months ago and did not reveal new or active lesions. This was the first possible exacerbation since the time of her diagnosis.

The patient was instructed to get laboratory evaluations done as soon as possible, including complete blood count, urinalysis, and urinary culture. The results of her complete blood count and urinalysis were reported to the office within 2 hours and were not significant for any signs of infection. The patient was called and advised to come to the office to be assessed for an MS relapse.

Her examination was significant for diminished strength in her legs, with 4/5 hip flexor strength bilaterally, 3.5/5 strength of left foot dorsiflexion, and increased tone in her lower extremities, Sensory examination revealed bilateral deep sensation impairment in the lower extremities. She had bilateral patellar hyperreflexia and a left Babinski sign. She had difficulty with tandem walk and had a Romberg sign. The patient was diagnosed with an MS relapse, and first-line therapy with IV methylprednisolone considered and declined, given her previous experience with IV methylprednisolone, so adrenocorticotropic hormone gel 1 mL (80 units) IM once a day for 10 days was prescribed.

On her follow-up visit 2 weeks later, she reported significant improvement in her symptoms, although she was not quite back to her baseline. On examination, she had normal muscle strength, sensory examination was unchanged, reflexes were unchanged, and urinary symptoms had dissipated. Her next follow-up visit took place 1 month later, at which time she reported being completely back to her baseline.

Comment. This case raises several issues, the first of which is the need to address whether an acute MS exacerbation has occurred and determine whether and how to treat it. This patient previously had a negative experience with systemic steroids, so adrenocorticotropic hormone was prescribed and was associated with more favorable tolerability.

A completely different issue is her current disease-modifying therapy compliance and efficacy. This subject needs to be carefully evaluated separately and independently of relapse treatment. Counseling on compliance and treatment adherence, follow-up MRI evaluations, and a potential change of disease-modifying therapy may be considered. (Note that MRI is not needed to confirm MS relapse, which is a clinical diagnosis, but MRI may be needed to address disease-modifying therapy adequacy.)

Case 6-2

A 38-year-old man with relapsing-remitting multiple sclerosis (MS) reported a 2-week history of new, and worsening, visual disturbances, swallowing issues, and balance and gait impairment. The patient said that his primary care physician had already treated him with IV steroids for 7 days, but his condition continued to deteriorate. He had no fever or sign of infection. A complete blood count, comprehensive metabolic profile, and urinalysis performed 2 days ago were within normal limits.

The patient had been diagnosed with MS 5 years ago after an initial episode of right leg weakness and urinary control issues. His initial symptoms suboptimally responded to IV methylprednisolone. After his initial diagnosis, he was started on interferon beta-1a 44 mcg subcutaneously 3 times a week but had poor compliance. He had two relapses the first year after his diagnosis. Natalizumab was initiated next, and he was stable on natalizumab for 3 years; however, 6 months ago, he decided to discontinue it because of the increased risk of progressive multifocal leukoencephalopathy given his 3 years of exposure to natalizumab and positive JC virus antibody status. He decided to ''go holistic'' and not start another disease-modifying therapy (in spite of receiving education about other options for disease-modifying therapy).

On examination, he had a bilateral internuclear ophthalmoplegia, impaired soft palate elevation, a flattened left nasolabial fold, increased limb tone, impaired coordination tasks bilaterally, and severe gait ataxia (he used a walker, while previously he had been walking without assistance).

He was admitted to the hospital for a series of plasma exchange treatments administered every other day, one volume exchange at a time. Initially, five sessions were planned. He started noticing improvement after the fourth session and continued improving after the fifth. The decision was made to add two more sessions (for a total of seven).

On the follow-up clinic visit 1 week after hospital discharge, he reported continued improvement. On examination, residual signs of a bilateral internuclear ophthalmoplegia and mild dysmetria and ataxia were seen; he was walking with a cane. Physical therapy was prescribed, and education on disease-modifying therapy was provided in the light of his recent history and future prognosis.

Comment. This case presents a patient with MS with a classic set of poor prognostic factors frequently associated with severe relapses and residual disability: male gender, pyramidal symptoms at the time of initial MS diagnosis, short time between relapses (this patient had two relapses in the first year after MS diagnosis), and early sphincter symptoms. His first relapse did not fully respond to systemic steroids, and the current relapse failed to respond. This particular relapse was rather severe, as it caused significant limitations and acute deficits. In this case, because of the need for robust intervention, the decision was made to use inpatient plasma exchange. In this patient, plasma exchange effects were not noted until after the fourth session, as response may not be immediate. Additional sessions were administered to achieve the best possible outcome, and once a clinical plateau was reached, the patient was discharged. Some improvement continued post–plasma exchange.

Case 6-3

Three months after the events described in **Case 6-1**, the patient described in that case reported overwhelming fatigue and bilateral leg weakness, tingling sensations, and stiffness. She denied any signs of infection. In response to a recommendation for laboratory evaluations, she inquired as to whether that would really be necessary since she had no current infectious or bladder symptoms and no infection had been found when she had her previous worsening. The neurologist explained that patients with multiple sclerosis may not always feel classic bladder infection symptoms, and if she had an infection, the relapse treatments could be harmful and ineffective. The patient reluctantly agreed to have a urinalysis done. The results revealed leukocyturia (40 white blood cells). A course of ciprofloxacin was prescribed. Ten days later, she reported complete resolution of her symptoms.

Comment. This is a classic case of pseudoexacerbation: symptoms mimicking a multiple sclerosis exacerbation were provoked by a urinary infection in this case. Note that this patient with spinal cord lesions did not have typical urinary tract infection symptoms. The office staff was not deterred by the previous negative infection workup results (**Case 6-1**) and did not deviate from routine laboratory evaluation, even when faced with the patient's frustration. The correct diagnosis was made and targeted antibacterial treatment was provided while potentially harmful treatments were avoided.

Although no absolute consensus exists on the long-term impact of relapses, their prognostic significance,[46] or even the significance of their treatment, from the patient's perspective MS exacerbations bring about a severe decline in quality of life; therefore, every effort should be undertaken to shorten these episodes.

CONCLUSION

Relapses of MS represent periods of acute immune inflammatory activity. MS exacerbations need to be recognized and treated in a timely manner. Recommended treatment options include systemic steroids, ACTH, and, for severe relapses not responding to either steroids or ACTH, plasma exchange.

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