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Brief Course of Ultra-High Dose IV Methylprednisolone in the Treatment of Multiple Sclerosis Exacerbations

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ABSTRACT

Despite the introduction of a number of effective disease modifying therapies (DMT) for multiple sclerosis (MS) over the past 25 years, a need remains for an effective method of treating breakthrough relapses, which impact disease progression. ACTH and corticosteroids have fulfilled this role for the past 50 years. However, based upon our current understanding of the cadence of an exacerbation, and its importance in the progression of MS, an alternative is proposed. This utilizes a very brief course of an ultra-high dose of intravenous methylprednisolone, adapted from the megadose protocol of methylprednisolone in acute spinal cord injury. Despite the known side effect profile of corticosteroids, and the ultra-high dose employed, the brevity in administration yields a well-tolerated, rapid resolution of the relapse.

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Introduction

Multiple sclerosis (MS) is a chronic central nervous system disease with no cure at the present time. It is believed to be an immune-mediated autoimmune disease, which has poorly defined triggers [1]. Although the destruction of the myelin sheath surrounding nerve fibers within the central nervous system has been considered the cornerstone pathognomonic feature of this disease, the primary molecular target of this aberrant immune response has defied identification to date. Combined with the consequence of collateral damage to nerve fibers this contributes to disease progression.

Epidemiologic studies have suggested an association between an environmental factor, perhaps an infectious agent, such as a virus, as a precipitant of this immune reaction [2]. Although numerous attempts to identify a specific etiologic pathogen have been made over the years, none has yet been identified. It is also believed the immune reaction in MS is strongly influenced by host genetic determinants, many of which are shared with other autoimmune disorders [3]. There are other epidemiologic factors of interest as well. At least twice as many women as men are affected by this disorder [4], suggesting the possibility of a hormonal role, specifically estradiol [5], in the immunopathogenesis of this disease. This presumably, but not solely, acts through its influence on the immune response characteristic of this disease.

Regarding age of onset, earlier studies have focused primarily on young adults, noting that symptoms most often present between the ages of 18 and 50 [6]. However, in recent years, exceptions to this have been identified, specifically in early childhood. Consequently, a great interest in pediatric MS has emerged [7]. This information raises a question regarding the actual onset of the underlying pathogenesis of this disorder in adults. It remains unclear as to whether the onset of clinical symptoms occurs concomitantly with the first pathologic expression of the disease, since MRI studies have demonstrated significant lesion activity without contemporaneous clinical consequence [8].

The clinical course of MS is of interest as well. There has been an effort to distinguish at least two major forms of MS. The predominant form is described as having a relapsing-remitting course [9], which characteristically occurs in the earlier phase of the disease. It is estimated that approximately half of these individuals go on to evolve into a secondary progressive phase of the disease [10]. Relapsing remitting MS is characterized by measureable fluctuations in circulating populations of immune cell subsets, which has been the target of the growing number of disease modifying therapies (DMT) that have become available since 1993 [11]. The effectiveness of the DMTs has been measured in terms of reduction in relapses, decline in MRI lesion burden and stability of functional clinical status. Unfortunately, there is no specific biomarker of MS disease activity, although the use of MRI has been the most acknowledged and utilized in this role to date [12]. However, recent studies have focused on an observed correlation with neurofilament light chains (NfL) in cerebrospinal fluid [13], and have also been detected in serum in a case control study, which allowed the observation of changes to be detected prior to clinical presentation [14]. This holds promise as a predictor of MS. It has been appreciated that there is a spectrum of expression regarding the frequency and severity of relapses, and their consequences of accumulated neurologic deficits and tissue atrophy (SPMS). The factors influencing this parameter have not been fully defined. Over the passage of time, clinical functional status, the accumulation of lesion burden, and atrophic changes, each as a consequence of previous immune attack, lead to transition into secondary progressive MS [15]. Like relapsing remitting MS, there is also a spectrum of expression of secondary

progressive MS. Newer classification makes a distinction between active SPMS and inactive SPMS [16]. There previously had been no effective treatment for this phase of the disease, although two new oral agents, siponimod (FDA News Release March 26, 2019) and cladribine (FDA News Release March 29, 2019), received FDA approval that included active secondary progressive MS [17].

Multiple clinical trials of candidate DMTs over the years have demonstrated that to have the most beneficial impact on the manifestations of secondary progressive MS, it is essential to treat the individual as early in the course as possible [18]. Delay in effective DMT treatment of MS inevitably will lead to progressive changes over time in predisposed individuals. What has been referred to as a progressive relapsing course may be recognition of relapses only after a degree of progression has occurred [19]. There is another clinical presentation of MS that has been recognized. Typically, this course has its onset later in life. Progressive spinal cord manifestations are the principal characteristic clinical feature of this presentation [20], which has been identified as primary progressive multiple sclerosis (PPMS). It is possible that this condition, currently thought of as a subset of MS presentation, is actually a distinct disorder, just as neuromyelitis optica (NMO) proved to be [21].

Prior to the development of disease modifying therapies, and even both during the pivotal clinical trials and after FDA approval, individual episodes of worsening of MS were treated with either the hormone ACTH, or a form of glucocorticoid [22]. PCTH was the first form of therapy demonstrated to be effective in shortening a clinical flare of MS (exacerbation), in a double blind, placebo-controlled therapeutic clinical trial [23]. Since it stimulated the production of corticosteroids, the latter were also administered therapeutically, as part of recognition of their clinical role in suppressing immune responsiveness [24]. ACTH may be administered by either subcutaneous or intramuscular administration. It has been recognized to have two separate mechanisms by which it may achieve therapeutic efficacy in MS. One is mediated through the direct stimulation of melanocortin receptors [25]. The other is through the induction of corticosteroids and their action. In contrast, the use of corticosteroids, which may be administered through multiple routes, provides greater utility since there are more available routes, forms and doses to administer [26]. The action of both ACTH and corticosteroids is to inhibit the production of inflammatory mediators [27], and to directly impact nerve impulse conduction possibly through a direct effect on the cell membrane [28], and through the reduction of interstitial edema [29].

Corticosteroids have been used clinically as an anti-inflammatory therapy in a number of immune-mediated diseases for many years. Clinical studies in the treatment of an MS exacerbation have been empirically developed. A general consensus of high-dose intravenous methylprednisolone, consisting of doses ranging from 500mg to 1000mg per day, for periods of three to five days, was empirically developed through several studies in the treatment of an acute MS relapse [30-32]. For this dose range, there has been consideration that oral and intravenous routes would have comparable efficacy. I do not believe the same therapeutic blood level can be achieved within a very short period of time utilizing the oral route of administration. Therefore, I have explored the feasibility of delivering an ultra-high dose of 10gm intravenous methylprednisolone within a 24-hour period. However, there are several issues that have been areas of concern in the therapeutic application of corticosteroids. Corticosteroid use can lead to a number of adverse events, each of which can be managed, but the clinician must be alert to their potential occurrence in order to react as rapidly as possible, or even preemptively [33].

For example, corticosteroids will impact blood sugar, so this must be monitored carefully, especially in those who are diabetic, or pre-diabetic. Similarly, there can be a rise in blood pressure and/or development of a tachyarrhythmia, or fluctuation in electrolytes, so these parameters must be monitored closely as well. Yet another concern is for those who are predisposed to a mood disorder, since at the least a sense of jitteriness is expected, but there are also those in whom a full blown manic episode may be precipitated. Dyspepsia is not uncommon either. Herpes zoster reactivation may be also triggered, causing shingles [34].

Fortunately, each of these conditions can be anticipated and addressed pre-emptively. This includes following vital signs, blood work (especially blood sugar and electrolytes) and EKG. If needed, 0.5mg lorazepam as a starting dose may be employed to address agitation, and 20mg famotidine for GI distress, can be provided. Additional interventions are available depending upon the response and needs of the patient.

There concerns occur most often with a more prolonged use of corticosteroids, rather than during a brief (one or two day) infusion. The most pronounced of these includes development of Cushingoid features [35]. with prolonged elevation of blood sugar levels, increased fat deposition on the back (hump back) and face (moon face), potential for cataracts, acne, skin changes such as striae, bruising and thinning, sodium and water retention, predisposition to infection, menstrual irregularities and hair loss in women, gynecomastia in men, decreased bone density and muscle atrophy.

In contrast, with the short term use of ultra-high dose corticosteroids, the likelihood for serious side effects is reduced since they are rapidly excreted [36]. Nevertheless, acute awareness of the potential side effect profile of corticosteroids is an important focus to reduce the potential downside of this form of immunotherapy, and healthcare providers must be vigilant in this regard.

That being said, it is my contention that for serious medical issues, such as treating an exacerbation (relapse) of MS, the best option is to provide the maximal dose of corticosteroid over the shortest possible course. The protocol of short term, megadose corticosteroids, was initially investigated in the treatment of acute spinal cord injury [37]. In their protocol, 30mg/kg was administered in the first hour, followed by 5.4mg/kg over each of the next 23 hours. For a 70kg person this would yield 10,794mg in 24 hours. This was well tolerated. Based upon this information, the protocol was adapted to deliver an ultra-high dose 10gm of intravenous methylprednisolone within a 24-hour period in the treatment of an acute exacerbation of MS.

Although short term ultra-high dose intravenous corticosteroid infusion may seem extreme at first glance, and may not be suitable for every patient, there are five points to consider in its favor. First, properly monitored, it has been safely administered in the treatment of acute spinal cord injury [38], and now MS (see below). Second, it affords the opportunity to rapidly and efficiently suppress the cytokine storm that drives the exacerbation-related inflammatory response [39]. Third, this is a compressed, single day protocol, which shortens the duration of symptoms overnight, rather than an evolving resolution over the currently utilized 5-day protocol administering 1gm per day. This practice can be initiated at any point after the onset of clinical symptoms or signs, but is

most effective when started closest to onset. Clinical improvement by utilizing the ultra-high dose protocol can limit the extent of neuroinflammatory tissue damage. Fourth, due to the manner of accelerated administration, the side effect profile associated with prolonged lower dose corticosteroid dosing is reduced. Fifth, there is a rapid reduction of tissue swelling [29], which also contributes to a more rapid resolution of symptoms and signs. The brief ultra-high dose intravenous protocol should be utilized with great caution in a newly diagnosed patient, with whom there is limited familiarity. However, rebound effects [40]. have not been observed regarding either recurrence of clinical symptoms or diminished adrenal function (electrolyte fluctuations, glucose) in patients treated in this fashion. Nevertheless, special concerns are needed for those with a propensity for a mood disorder, cardiac arrhythmia, dyspepsia, diabetes or renal disease.

This protocol should be administered within a hospital setting for safety issues regarding monitoring clinical status, mood, blood pressure, cardiac rhythm, blood sugar and electrolytes. Preemptive interventions by concomitant administration of lorazepam and famotidine help to reduce to occurrence of agitation and dyspepsia, which are common side effects of corticosteroid administration.

Intravenous (IV) Administration

Dosing Protocol 1 (one day) 10gm option, day 1
Dosing Protocol 2 (two days) 5gm option, day 1, and 5gm day 2

The vials of methylprednisolone have been administered utilizing either 500cc of D5W or D5/0.5N saline as the diluent. Unlike the stepwise administration used in the spinal cord injury protocol, the medication was programmed to run over 20 hours.

I have treated over 50 patients utilizing this protocol, usually as an inpatient, but also within an infusion center setting, with excellent clinical results. The issues of monitoring for mood disorder and cardiac arrhythmia were the two most critical that required very close monitoring of the treatment. Other parameters were routinely monitored successfully, and uneventful.

Generally, patients experienced rapid resolution of clinical neurologic symptoms, literally overnight, and tolerated this protocol without adverse reactions. However, close monitoring is nevertheless warranted. Patients have been successfully treated utilizing this protocol overnight and safely discharged after the 20-hour period from time of admission, clinically stable. A steroid taper was not necessary. The methylprednisolone at this dose is believed to be functioning pharmacologically rather than physiologically [37]. Despite the appropriate emphasis on clinical use of MRI to assess lesion activity, careful clinical judgement in the selection of patients for this treatment protocol is imperative. If there are concerns regarding mood, cardiac status, blood pressure, blood sugar or electrolytes, appropriate adjustments, including stopping the protocol are warranted in order to reassess the status of the patient.

In summary, the rapid infusion of as much as 10gm of methylprednisolone in a 20-hour period can successfully be accomplished in the treatment of an acute exacerbation of MS. The benefit of this brief infusion of ultra-high dose methylprednisolone in rapidly terminating the exacerbation-related cytokine storm and inflammatory response of the exacerbation produces an immediately effective clinical response [39]. Rebound of clinical neurologic symptoms or metabolic symptoms affecting electrolytes or glucose have not been observed [40]. Monitoring for possible side effects of this dose administration is imperative and cannot be overemphasized.

This brief ultra-high dose protocol has provided rapid beneficial results in this series of patients experiencing an acute exacerbation of MS. Response to treatment was essentially overnight. The brief, ultra-high dose protocol provides an effective alternative, clinically permissible, in the treatment of MS exacerbation and other disorders associated with cytokine storm [41]. such as Covid-19, where a more prolonged course with lower doses could yield intolerable or even detrimental clinical responses [42].

References

1. Martin R, McFarland HF, McFarlin (1992) DE. Immunological aspects of demyelinating diseases. Ann Rev Immunol 10:153-187.
2. Steiner I, Nisipianu P, Wirguin I (2001) Infection and the etiology and pathogenesis of multiple sclerosis Curr Neurol Neurosci Rep 1: 271-276.
3. Didonna A, Oksenberg JR (2015) Genetic determinants of risk and progression in multiple sclerosis Clin Chim ActaClin Chim Acta 449: 16-22.
4. Boström I, Landtblom AM (2015) Does the changing sex ratio of multiple sclerosis give opportunities for intervention? Acta Neurol Scand. 132: 42-45.
5. Gold SF, Voskuhl RR (2009) Estrogen treatment of multiple sclerosis. J Neurol Sci. 286: 99-103.
6. Confavreux C, Vukusic S (2006) Age at disability milestones in multiple sclerosis. Brain 129: 595-605.
7. Alroughani R, Boyko A (2018) Pediatric multiple sclerosis: a review. BMC Neurol. 18:27 https://doi.org/10.1186/s12883-018-1026-3.
8. McFarland HF, Stone LA, Calabresi PA, et al. (1996) NRI studies of multiple sclerosis: Implications for the natural history of the disease and for monitoring effectiveness of experimental therapies 2: 198-205.
9. Weinshenker BG, Bass B, Rice GP, et al. (1989) The natural history of multiple sclerosis: A geographically based study. I. Clinical course and disability. Brain 112: 133-146.
10. Confavreux C, Vukusic S (2006) Natural history of multiple sclerosis: A unifying concept. Brain 129: 606-616.
11. Costello K, Kalb R (2019) The use of disease modifying therapies in multiple sclerosis: Principles and current evidence. A consensus paper by the Multiple Sclerosis Coalition. Updated June 2019 http://ms-coalition.org/the-use-of-disease-modifying-therapies-in-multiple-sclerosis-updated/.
12. Barnett Y, Garber JY, Barnett MH (2020) MRI biomarkers of disease progression in multiple sclerosis: Old dog, new tricks? Quant Imaging Med Surg 010: 527-532.
13. Varhaug KN, Torkildsen Ø, Myhr K-M, et al. (2019) Neurofilament light chain as a biomarker in multiple sclerosis. Front. Neurol 10:338.
14. Bjornevik K, Munger KL, Cortese M, et al. (2020) Serum neurofilament light chain levels in patients with presymptomatic multiple sclerosis. JAMA Neurol 77:58-64.
15. Prineas JW, Kwon EE, Cho E-S, eta al. (2001) Immunopathology of secondary progressive multiple sclerosis. Ann Neurol 50:646-657.
16. Sellebjerg F, Börnsen L, Ammitzbøll C, et al. (2017) Defining active progressive multiple sclerosis. Mult Scler 23: 1727-1735.
17. Luzzio C (2020) Multiple sclerosis treatment & management. Medscape. Updated April 30 https://emedicine.medscape.com/article/1146199-treatment.

18. Cerqueira JJ, Compston DAS, Geraldes R, et al. (2018) Time matters in multiple sclerosis: Can early treatment and long-term follow up ensure everyone benefits from the latest advances in multiple sclerosis? J Neuol Neurosurg Psychiatry 89:844-850.
19. Kremrnchutzky M, Cottrell D, Rice G, et al. (1999) the natural history of multiple sclerosis: a geographically based study: 7. Progressive-relapsing and relapsing-progressive multiple sclerosis: A re-evaluation. Brain 122: 1941-1950.
20. Cottrell DA, Kremenchutzky M, Rice GPA, et al. (1999) the natural history of multiple sclerosis: A geographically based study 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 122: 625-639.
21. Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. (2007) the spectrum of neuromyelitis optica. The Lancet Neurology 6:805-815.
22. Silverman M, Sternberg EM (2012) Glucocorticoid regulation of inflammation and its behavioral and metabolic correlates: From HPA axis to glucorticoid receptor dysfunction. Ann NY Acad Sci 1261:55-63.
23. Rose AS, Kuzma JW, Kurtzke JF, et al. (1970) Cooperative study in the valuation of therapy in multiple sclerosis: ACTH vs. placebo Final Report. Neurology 20:1-59.
24. Nelson HS (2003) Leung DYM, Bloom JW. Update on glucocorticoid action and resistance. Curr Rev Allergy Clin Immunology 111: 3-32.
25. Wang W, Guo D-Y, Lin Y-J, et al. (2019) Melanocortin regulation of inflammation. Front Endocrinol 10:683.
26. Zoorob RJ, Gender D (1998) A different look at corticosteroids. Am Fam Physician 58: 443-450.
27. Liberman AC, Budziñski ML, Sokin C, et al. (2018) Regulatory and mechanistic actions of glucocorticoids on T cells and inflammatory cells. Front Endocrinolhttps://doi.org/10.3389/fendo.2018.00235.
28. Abraham IM, Meerrlo P, Luiten PGM (2006) Concentration dependent actions of glucocorticoids on neuronal viability and survival. Dose Response 4: 38-54.
29. Betz AL, Coester HC (1990) Effects of steroids on edema and sodium uptake of the brain during focal ischemia in rats. Stroke 21:1199-1204.
30. Durelli L, Cocito D, Riccio A, et al. (1986) High-dose inrtravenous methylprednisolone in the treatment of multiple sclerosis: Clinical-immunologic correlations. Neurology 36: 238-243.
31. Beck RW, Cleary PA, Trobe JD, et al. (1993) The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. N Engl J Med 329:1764-1769.
32. Liu S, Liu X, Chen S, et al. (2017) Oral versus intravenous methylprednisolone for the treatment of multiple sclerosis relapses: A meta-analysis of randomized controlled trials. PLoS ONE https://doi.org/10.1371/journal.pone.0188644 12: e0188-644.
33. Stanbury RM, Graham EM (1998) Systemic corticosteroid therapy - side effects and their management. Br J Ophthalmology 82:704-708.
34. Marra F, Lo E, Kalashnikov V, et al. (2016) Risk of herpes zoster in individuals on biologics, disease-modifying antirheumatic drugs, and/or corticosteroids for autoimmune diseases: A systematic review and meta-analysis. Open Forum Infectious Diseases https://doi.org/10.1093/ofid/ofw205 3:205.
35. Arnaldi G, Angeli A, Atkinson AB, et al. (2003) Diagnosis and complications of Cushing's syndrome: A consensus statement. J Clin Endocrinol Metab 88: 5593-5602.
36. Al-Habet SM, Rogers HJ (1989) Methylprednisolone pharmacokinetics after intravenous and oral administration. Br J Pharmac 27:285-290.
37. Young W (1990) Editorial NASCIS (National Acute Spinal Cord Injury Study). J Neurotrauma 7: 113-114.
38. Bracken MB, Shepard MJ, Collins WF, et al. (1990) A randomized controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cords injury: Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 322:1405-1411.
39. Lee DW, Gardner R, Porter DL, et al. (2014) Current concepts in the diagnosis and management of cytokine release syndrome, Blood 124:188-195.
40. Good TA, Benton JW, Kelley VC (1959) Symptomatology resulting from withdrawal of steroid hormone therapy. Arthritis & Rheumatism 2: 299-321.
41. Behrens EM, Koretzky GA (2017) Cytokine storm syndrome: looking toward the precision medicine era. Arthritis & Rheumatology 69:1135-1143.
42. Cutolo M, Seriolo B, Pizzorni C, et al. (2008) Use of glucocorticoids and risk of infections. Autoimmunity Rev Detrimental response to prolonged steroid (Covid-19?) 8:153-155.