OPINION

Does the Rhythmic Pulse Corticosteroid (methylprednisolone) Treatment in Multiple Sclerosis Patients Prevent or Reduce the Evolution into Persistent Black Holes?

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ABSTRACT

The availability of oral methylprednisolone (MP) (for example, a capsula to 100mg MP) allows rapid oral administration of high-dose MP in relapsing multiple sclerosis. There are no significant differences in clinical, radiological outcomes for oral or intravenous administration. Timely treatment could prevent the conversion of "acute black holes" into persistent "black holes". The concomitant administration of high dose vitamin D with the aim of achieving physiological serum VD levels prevents side effects on bone metabolism. High 25(OH)D serum levels are associated with reduced relaps rates and reduced active lesions on MRI. The oral dose of 1250 mg MP/24 hours equals 1000 mg intravenous MP.

Key words: Relapsing-remitting multiple sclerosis, Black holes, rhythmic methylprednisolon pulse therapy, oral methylprednisolone, Supplementation of Vitamin D

INTRODUCTION

An important goal of multiple sclerosis (MS) therapy is the prolongation of the conversion from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) because the conversion is associated with a relatively poor prognosis. In the clinical practice, SPMS is typically diagnosed retrospectively. This objective definition of SPMS based on the expanded disability status scale (EDSS) and information about prior relapses provides a tool for a reliable, accurate, and timely diagnosis that requires a very short confirmation period.[1] Di Gregorio *et al*. have been able to show that the treatment of MS relapses with high-dose methylprednisolone (MP) reduces in the magnetic resonance imaging (MRI) the evolution of contrast-enhancing lesions into persistent black holes (pBHs).[2] pBHs in T1-weighted images (MRI) reflect brain tissue loss in people with multiple sclerosis (PwMS). The administration of MP can limit the central nervous system (CNS) inflammatory attack by targeting several pathophysiological mechanisms, (1) the activation of T cells, T cells inhibit the formation of proinflammatory substances (inhibition of transcription) and promote anti-inflammatory messengers (transcription promotion), (2) inflammatory cytokine cascade, (3) the extravasation of immune cells, and (4) the cytotoxic effects of nitric oxide and TNF-α.[3] MP has direct effects on the migration of immune cells across the blood–brain barrier. The stop of SPMS by disease-modifying therapies (DMTs) is not complete. None of the currently available treatment (DMTs) can completely avoid exacerbation.

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METHYLPREDNISOLONE PULSE THERAPY FOR THE PREVENTION OF NEUROAXONAL DAMAGE IN CLINICAL PRACTICE

It would be debatable whether the administration of a short course of high-dose steroid (3–5 days 1000 mg/day MP), oral (o) or intravenous (iv), has any long-term functional benefit in the rhythm of 3–4 times a year. PwMS can develop acute lesions without clinical symptoms. If only the clinical events of MP therapy lead the way in patient monitoring, MS may progressively progress unrecognized.

Overall, the efficacy of MS treatment seems to be higher in the earlier stages of RRMS and decreases over time. The indication for a cyclic MP administration could be facilitated if osteopontin (OPN) was used as a biomarker of inflammation. OPN increase in serum (and cerebrospinal fluid) indicates active inflammation. It is an extracellular matrix protein involved in a variety of physiologic functions and pathological states and is widely expressed in immune cells, including T cells, dendritic cells, macrophages, and natural killer cells and contributes to inflammation through increasing production of IL-12, IL-17, and interferon gamma and inhibiting expression of IL-10.[4-6] If serum OPN is elevated in relapses, early management (MP administration) could successfully curb the transition to SPMS. In monitoring MS treatment, serum biomarker neurofilament light chain may also be useful for detecting subclinical disease activity.[7-9]

In the context of personalized medicine for MS and the wide individual variation in clinical presentation, disease course, and responses to treatments, these questions arise. The availability of oral MP could be an instrument in PwMS with RRMS. No inpatient stays of PwMS, lower cost, and logistics, and because it not interferes with family and social life, is more convenient, and avoids the contact with needles. Studies indicated some efficacy of MP pulse therapy in PPMS and SPMS.[10,11] Ramo-Tello *et al*. provides in their study evidence that oMP is not inferior to iv MP in reducing EDSS and MRI lesions at 4 weeks for MS relapses and is equally well tolerated.[11,12] Martinelli *et al*. administered 1 g oMP × 5 days or 1 g iv MP × 5 days.[12] However, in the trial of Ramo-Tello *et al*. bioequivalent doses of oMP and i.v.MP were given, not identical doses. The oMP dose of 1250 mg/24 h for 3 days corresponds to the same blood levels as the iv dose. MP has an oral bioavailability of 80%. The overall incidence of treatment-emergent adverse events reported by patients until day 28 was equal in the oral and i.v.MP group, only for insomnia, which had increased in the oral group.[13]

IMPLICATIONS FOR PREVENTION OF ADVERSE EFFECTS OF A CYCLIC MP THERAPY

Prevention or treatment of glucocorticoid-induced osteoporosis should be considered in all patients who receive MP. It has been observed higher incidence of fracture rates among adults with PwMS, risk of hip fracture was 3–4-fold that controls.[14,15] At the same time, a low Vitamin D (VD) status at diagnosis is associated with an early conversion to secondary progressive MS. A daily VD supplementation for the most patients between 2000 and 5000 IE/day should be given with the aim of a 25(OH)D levels between 40 and 60 ng/ml (100–150 nmol/l).[16] In PwMS, high-dose supplementation up to 5000–10,000 IU/day is not associated with harm and may be of benefit in terms of both fracture risk and MS pathogenesis (without contraindications).[17]

CONCLUSION

Patients with highly active MS and DMTs who are nevertheless symptomatic for a clinical relapse may undergo repeated MP-pulse therapy. The protective effect of MP as for relapse treatment may have some interesting implications in the clinical practice since it is possible to hypothesize that the treatment of PwMS with contrast-enhancing lesions could be useful not only to reduce the duration of relapse symptoms but also to reduce the probability of CNS tissue loss.[2] It is hoped that these efforts will delay the transition to SPMS. A long-term study with pulsed corticosteroid treatment in PwMS to stabilize disease activity as adjunct therapy to DMTs in combination with Vitamin D supplementation is essential. These combinations would be safe and most PwMS with disease activity tolerated MP as an adjunct to Vitamin D. The availability of the oral steroid (MP) allows a quick response of the medical community to relapses and facilitates cyclic MP administrations. The estimated time of about 15 years should not pass until the results of the research lead to a clinical implementation.

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