Pulsed Intravenous Methylprednisolone Therapy in Progressive Multiple Sclerosis: Need for a Controlled Trial

More than half of patients with relapsing-remitting multiple sclerosis (MS) develop a progressive illness in about 10 to 15 years (secondary progressive MS), and 10% to 15% of all patients with MS enter the progressive stage from onset (primary progressive MS). After a patient reaches level 4 on the Expanded Disability Status Scale,[1] the rate of progression becomes identical in primary and secondary progressive cases. This suggests a common mechanism for progression, which may be related to axonal abnormalities. For progressive forms of MS, unless they are associated with rapid progression and evidence of inflammation, there is no accepted treatment. In our experience, a subset of patients with progressive MS shows an objective and measurable response to intravenous methylprednisolone sodium succinate (IVMP) treatment. The aim of this letter is to report the effects of pulsed IVMP therapy given for years in a subset of patients with progressive MS.

Using the central records system of the Mayo Clinic (Rochester, Minn), we reviewed the medical records of all patients (490) who received IVMP treatment as outpatients for MS between 1990 and 2002. Inclusion in our study required (1) primary or secondary progressive MS; (2) no acute exacerbation for 1 year; (3) no injectable or oral immunomodulators for 1 year; (4) pulsed IVMP at a dose of 1g/mo or 3 doses of 1 g/d every 3 months; (5) pulsed IVMP therapy for at least 1 year; (6) documented semiannual follow-up examinations; and (7) documented worsening of neurologic examination findings in the year preceding therapy. Results of all patients meeting these criteria are reported. Data including demographic (sex, age at onset, and age at first pulsed IVMP treatment) and clinical characteristics (neurologic examination findings and magnetic resonance imaging data when available) were obtained. The Mayo Clinic institutional review board (No. 1599-02) approved the study. Standard neurologic examinations were performed for each patient, and data from standard questionnaires (regarding fatigue, bowel and bladder functions, and mobility) were used. A 1-point change in each component of the neurologic record and Functional System Scale[1] was used to determine worsening or improvement. Changes had to be confirmed by the results of at least 2 examinations done 6 months apart. Scores that were not consistently worsening or improving by 1 point were considered unchanged. Our data (**Table**) are categorized as improved, worse, or unchanged. At every visit, data were obtained by a blinded examiner. The Table shows the treatment effect at the last neurologic examination.

Ten patients met the inclusion criteria (Table). The mean±SD age at MS onset was 42.0±13.5 years. The mean±SD age at pulsed IVMP treatment initiation was 47.0±14.2 years. The mean±SD length of pulsed IVMP use was 3.8±2.6 years. The male-female ratio was 3:2. In 5 patients, other treatments (oral prednisolone, interferon alfa, cyclophosphamide, and interferon beta) failed to slow the rate of progression. Of the 10 patients, 9 did not develop acute exacerbation during the course of IVMP treatment. At 1 year following pulsed IVMP treatments, fatigue improved in 6 patients and worsened in 2. Spasticity improved in 9 (90%) of 10 patients; motor strength improved in 8 (80%) of 10. Motor improvement was confined to pyramidal functions. Ataxia worsened in 6 (60%) of 10 patients and improved in none. Bowel and bladder problems worsened in 6 (60%) of 10. One patient developed a new clinical attack of MS associated with gadolinium enhancement and was switched to interferon beta therapy. Another patient requested to switch to interferon therapy because of adverse effects related to mood and sleep hygiene. All patients were monitored for the development of osteoporosis. Patients were encouraged to take multivitamin and calcium supplements.

The results of this small study suggest that there may be a treatment effect of pulsed IVMP in a subset of patients with progressive MS. The generally accepted view is that steroids do not have long-term effects on the progression of MS. However, in the Optic Neuritis Treatment Trial,[2] the development of clinical MS was delayed by the use of intravenous steroids. This was unexpected and suggests potential neuroprotective or extended immunomodulatory effects of IVMP. More recently, a crossover trial of 35 Italian patients with a "primarily chronic progressive form of multiple sclerosis"[3(p193)] who were receiving IVMP showed improvement lasting up to 90 days after treatment. In another trial, 18 of 32 patients with chronic progressive MS showed a measurable improvement in Expanded Disability Status Scale scores by a mean of 0.56 at 12 months of follow-up after IVMP treatment.[4] In a novel study, parameters related to the progression of MS were followed for 5 years in 88 patients receiving pulsed IVMP either independent of relapses or for relapses only.[5] The study was unblinded and did not have a placebo arm. Pulsed IVMP therapy delayed the formation of T1 black holes, which are considered compatible with areas of axonal loss. The treatment also slowed the progression of disability and had a protective effect on atrophy.

A mechanism independent of demyelination may be responsible for progressive MS. The magnetic resonance imaging marker that correlates best with disability is the T1-hypointense lesion load. We propose that pulsed IVMP therapy may have axonal protective effects. This may be related to enhanced remyelination and consequential axonal protection.[6] Direct neuroprotective effects of corticosteroids have been observed in animal experiments and are partially explained by their trophic and proliferative effects on astrocytes. Steroids also suppress nitric oxide levels and attenuate the aberrant expression of certain proteins that are indicators of abnormal synaptogenesis, denervation, and muscle atrophy.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

Pulsed Intravenous Methylprednisolone Treatment in a Subset of Patients With Progressive Forms of Multiple Sclerosis*

Characteristic	Patient No. 1	2	3	4	5	6	7	8	9	10
Sex	F	F	M	F	M	M	M	M	M	F
Age at MS diagnosis, y	24	27	55	58	62	33	34	35	42	50
Age at first treatment, y	36	37	65	69	65	34	36	35	44	52
MS type	PP	PP	PP	PP	PP	SP	SP	SP	SP	SP
Previous failed treatments	Interferon beta	Interferon beta	Interferon alfa	None	Oral prednisolone	None	None	None	Cyclophosphamide	None
IVMP dose	3 g every 3 mo	3 g every 3 mo	1 g/mo for 4 y, 3 g every 3 mo	3 g every 3 mo	3 g every 6 mo	3 g every 3 mo	3 g every 3 mo	3 g every 3 mo	3 g every 3 mo for 2 y, 1 g/mo	3 g every 3 mo
IVMP treatment duration	9 y, ongoing	1½ y, ongoing	6 y, ongoing	1 y, ongoing	4 y, ongoing	3 y	2 y, lost to follow-up	1 y, interferon beta	5 y, ongoing	5 y, then new attack of MS with interferon beta
Fatigue	No change	No change	Improved	Improved	Improved	Worse	Worse	Improved	Improved	Improved
Spasticity	Improved	Improved	Improved	Improved	Improved	Improved	Improved	No change	Improved	Improved
Motor strength	Improved	Improved	Improved	Improved	Improved	Improved	No change	Improved	Improved	Improved
Gait	Improved	Improved	Improved	Improved	Improved	Improved	Improved	No change	Improved	Improved
Ataxia	Worse	Worse	No change	Worse	Worse	Worse	No change	Worse	No change	No change
Bladder/bowel problems	Worse	No change	Worse	Worse	No change	Worse	Worse	No change	Worse	No change
Adverse effects	None	None	None	None	None	Sleep problems	None	Sleep problems, psychiatric problems	None	None
MRI before	ND	No gadolinium-enhancing lesions	No gadolinium-enhancing lesions	ND	No gadolinium-enhancing lesions	No gadolinium-enhancing lesions	ND	ND	No gadolinium-enhancing lesions	No gadolinium-enhancing lesions
MRI later	ND	No change (2 y)	No change (1 y)	ND	No change (2 y)	No change (1 y)	ND	ND	Some progression, no gadolinium-enhancing lesions (2 y)	No change (2 y), new gadolinium-enhancing lesions (5 y)

Abbreviations: IVMP, intravenous methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; ND, not done; PP, primary progressive; SP, secondary progressive.

*Improvement or worsening was defined as a confirmed 1-point change in the standardized Mayo Clinic (Rochester, Minn) neurologic examination results comparing function at the initiation of IVMP treatment to that at the last follow-up visit.

The fact that certain neurologic functions improved in our study (spasticity and motor weakness), whereas others did not (ataxia and bladder dysfunction), argues against a placebo effect of IVMP. We conclude that a large, long-term, placebo-controlled, double-blinded phase 3 study of pulsed IVMP therapy in progressive MS is warranted.

Istvan Pirko, MD
Moses Rodriguez, MD

This study was supported by grants RO1-NS24180, RO1-NS32129, RO1-NS38468 from the National Institutes of Health, Bethesda, Md.

Correspondence: Dr Rodriguez, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (rodriguez.moses@mayo.edu).

1. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
2. Beck RW, Cleary PA, Trobe JD, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis: the Optic Neuritis Study Group. *N Engl J Med*. 1993;329:1764-1769.
3. Cazzato G, Mesiano T, Antonello R, et al. Double-blind, placebo-controlled, randomized, crossover trial of high-dose methylprednisolone in patients with chronic progressive form of multiple sclerosis. *Eur Neurol*. 1995;35:193-198.
4. Bergamaschi R, Versino M, Raiola E, Citterio A, Cosi V. High-dose methylprednisolone infusions in relapsing and in chronic progressive multiple sclerosis patients: one year follow-up. *Acta Neurol (Napoli)*. 1993;15:33-43.
5. Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology*. 2001;57:1239-1247.
6. Pavelko KD, van Engelen BG, Rodriguez M. Acceleration in the rate of CNS remyelination in lysolecithin-induced demyelination. *J Neurosci*. 1998;18:2498-2505.

Comparison of Magnetic Resonance Imaging Abnormalities in Japanese Encephalitis and Acute Necrotizing Encephalopathy of Childhood

I read with great interest the article by Kalita et al.[1] In recent years, Japanese encephalitis (JE) has been well controlled with immunization in Taiwan, similar to Japan and Korea, as stated by Kalita and colleagues. Few Taiwanese children now develop JE; however, adult cases are increasing.

For children living in areas endemic to JE, especially Taiwan and Japan, acute necrotizing encephalopa-

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.