Safety of Long-term Intrathecal Methotrexate Therapy in Progressive Forms of Multiple Sclerosis

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INTRODUCTION

Progressive forms of multiple sclerosis (MS) are characterized by gradual worsening of disability with a relative lack of acute clinical and radiographic changes. Although poorly understood, the pathophysiology of progressive disease may be primarily restricted to the central nervous system with less contribution from peripheral immune cells. Few systemic treatment options have been shown to successfully treat progressive MS and even fewer drugs have been examined in the most severely disabled patients (EDSS $\geq$ 6.0). In 2010, we reported results of intrathecal (IT) administration of methotrexate (MTX) in the treatment of progressive MS for up to 8 treatments. However, the long-term safety of this regimen has not been reported. This study is a retrospective chart analysis of patients who have had 18 IT MTX or more treatments (3- 6 years) at our center in order to further examine the long-term safety and tolerability of IT MTX in this select cohort of advanced MS patients.

METHODS

This study was approved by the IRB committee of Roosevelt Hospital, New York. Patient consent was obtained prior to each administration of MTX and prior to the review for this study.

Patient Selection

Patients were selected at the discretion of the treating physician for IT MTX treatment if they fulfilled the following criteria:

1) Clinically-definite, progressive MS (PPMS or SPMS)
2) Prior treatment with at least 3 FDA-approved treatments for at least one year
3) Active disease with worsening of EDSS in the year preceding initiation of ITMTX

Patient Treatment

Methotrexate at a dose of 12.5 mg was administered via lumbar puncture or an access port of a surgically implanted pump every 8-11 weeks for a period of 3-6 years (range of 18 to 40 treatments). Patients had the option to discontinue treatment at any time.

Patient Assessment

Thirty three patients (27 SPMS and 6 PPMS) were clinically assessed every two months while receiving IT MTX. The assessment included EDSS, documentation of infections, any other adverse events, as well as hospitalizations. Complete blood count and MRI scans were also intermittently performed.

RESULTS

General Considerations

This study is not placebo-controlled and is not blinded. However, selection of severely disabled patients (mean starting EDSS of 6.4) in our view minimized the bias associated with remissions frequently seen early in disease. Also the duration of the study of up to 6 years also reduced bias that may be introduced by shorter duration studies.

Duration of treatment

About 50% of our patients (16 of 33) received at least 36 to 40 doses of IT MTX over a period of 72 to 80 months and only 6 patients (18%) were treated with less than 25 doses all of whom had at least 36 months of therapy.

Safety and Tolerability

The most notable finding was that over a sustained period of time this invasive treatment was remarkably well tolerated with minimal if any adverse events reported by any patient. Headaches occurred at least once in 12% of patients (possibly minimized by the use of 25-gauge spinal needle) and transient fatigue was reported by 6% of patients. No cases of MTX-associated leukoencephalopathy were seen, perhaps due to the less frequent dosing than in MTX-treated oncology patients. There were no serious adverse events reported and no hospitalizations related to this therapy. No CNS or other infections occurred and no deaths were reported.

Change of EDSS on Treatment

The mean EDSS for all patients at initiation of therapy was 6.4 and after 18-40 treatments the mean EDSS was 6.6. Over the duration of the study, 48% of patients had improvement or no decline in their EDSS scores. The remaining patients had an average EDSS increase of 0.68 points.

When analyzed by MS subtype, 16 out of 27 SPMS patients had no measurable clinical worsening. The remaining SPMS patients had an average EDSS increase of 0.2. One PPMS patient remained completely stable with the other 5 patients worsening by a mean of 0.7 points.

CONCLUSIONS

1. Pulsed IT MTX therapy was well tolerated over a period of 3-6 years in MS patients with progressive disease; no serious adverse events were noted.
2. Although this study was not controlled, given the poor natural history of severe progressive treatment-resistant MS, there was evidence of disease stabilization in most patients.
3. These findings support the use of IT MTX treatment as an extremely inexpensive and relatively safe treatment for progressive forms of MS, although additional controlled studies are needed to better establish this form of therapy.

There are no pertinent disclosures.