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ORIGINAL COMMUNICATION

Intrathecal methotrexate treatment in multiple sclerosis

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Abstract This study reports on the feasibility of using intrathecal methotrexate (ITMTX) in treatment unresponsive multiple sclerosis (MS) patients with progressive forms of the disease. A retrospective, open-label, chart review analysis was conducted following patients ($n = 121$) with MS for up to eight treatments given every 8–11 weeks. Patients were considered for ITMTX treatment if they were unresponsive to or intolerant of FDA-approved treatments. There was a 1 year follow-up after their eighth or last treatment (if discontinued earlier). Patients underwent neurological assessments and expanded disability status scale (EDSS) evaluations. No serious adverse effects were noted during the study period. In 87 secondary progressive MS patients, EDSS scores were stable or improved in 89%, with significantly improved mean EDSS post-treatment compared to baseline ($P = 0.014$). Of 34 primary progressive patients, EDSS scores were stable in 82%, with no significant progression in EDSS post-treatment compared to baseline. ITMTX may have a beneficial role in progressive forms of MS and is well tolerated with no serious adverse events.

Keywords Methotrexate · Intrathecal · Cerebrospinal fluid · Multiple sclerosis

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Introduction

Multiple sclerosis (MS) is characterized pathologically by demyelination, axonal loss, and glial scar formation. Clinically, most patients have a relapsing-remitting course (RRMS) that over time may become secondarily progressive (SPMS). About 15% of patients, however, have a progressive course from onset (PPMS) [24]. In the past decade, several treatments have been approved by the Food and Drug Administration (FDA) for use in RRMS and SPMS. However, these therapies are not effective for all cases of RRMS. Furthermore, current SPMS treatments may have a therapeutic effect for the early inflammatory phase of the disease, but become increasingly ineffective for the later presumably degenerative phase of established SPMS [3, 17, 21]. For PPMS, there is currently no FDA-approved treatment. Thus, more effective therapies need to be developed for treatment unresponsive RRMS/SPMS and PPMS.

Methotrexate (MTX), an antimetabolite, has been in clinical use since 1948 when it was found to produce temporary remission of acute childhood leukemia [2]. Because of its indirect immunosuppressive effects, MTX is used in treating autoimmune conditions such as rheumatoid arthritis and psoriasis [6, 27]. Low dose oral MTX (7.5 mg weekly) is efficacious, albeit minimally, in slowing deterioration in patients with SPMS [12]. However, it is possible that because the disability associated with SPMS/PPMS is primarily spinal in origin, MTX given orally is a suboptimal route of administration. In an analogous clinical setting of spinal spasticity, intrathecal baclofen (ITB) compared to oral baclofen is better tolerated and highly effective in significantly lower doses than when used orally [4, 23]. The safety of intrathecal MTX (ITMTX) has been demonstrated by its widespread use in treating childhood

leukemia with meningeal involvement [2]. The use of ITMTX in MS has not been investigated.

This retrospective chart review analysis reports on the safety, tolerability, and efficacy trends of ITMTX use in treatment-resistant, progressive forms of MS.

Materials and methods

Patient selection

Institutional review board approval was obtained to conduct a chart review of all patients treated with ITMTX between the years of 2002 and 2005. A total of 121 MS patients (87 SPMS and 34 PPMS) were included in this open-label, retrospective study. Patients were only considered for ITMTX therapy if the following criteria were met: age over 18 years, clinically definite diagnosis of MS, prior treatment with at least three FDA-approved disease modifying agents (each for at least 6 months), and active disease. Active disease was defined by the presence of any one of the following criteria in the year preceding ITMTX therapy: (1) one or more relapses documented by neurologist examination, (2) change in 0.5 point or greater in expanded disability status scale (EDSS) [19] score, and (3) change in MRI, specifically a change in the number or size of lesions or the presence of gadolinium-enhancing lesions. Exclusion criteria for ITMTX treatment included pregnancy, active infection, significant associated medical condition such as heart disease, and known allergy to MTX. These criteria were set prior to study commencement. All patients included in the study received at least two ITMTX treatments and were studied for a total of eight treatments. All patients were followed for a year after treatment cessation or completion to monitor post-treatment sequelae.

Patient demographics

The study population was approximately two-thirds female (68%) and one-third male (32%) (Table 1). Of the SPMS patients, 75% were female and 25% male. The PPMS patient population was 50% female and 50% male. The age range was 30–74 years old, with the youngest female being 32 years and the oldest female 74, while the youngest and oldest males were 30 and 74, respectively. Baseline EDSS scores at treatment start ranged from 3.0 to 9.0.

Table 1 Patient demographics

Patient demographics	*n*
Total number of patients	121
Age range	50.7 ± 10.5 (range 30–74)
Total males	39 (32%)
Total females	82 (68%)
SPMS	87 (M: 25% F: 75%)
PPMS	34 (M: 50% F: 50%)
Baseline EDSS	6.17 ± 1.15
Number of treatments	761
Continuing treatment (8 or more)	66
Discontinued treatment (total *n*)	55
Discontinued because of hold (eventually had eight treatments)	15

Values reported as mean ± SD or *n*

SPMS secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *EDSS* Kurtzke expanded disability status scale

Treatment protocol

A baseline complete blood count (CBC) with differential was drawn on all patients prior to starting treatment. After obtaining informed consent to perform the procedure, a physician administered 12.5 mg of ITMTX via lumbar puncture with a 25 gauge needle (89 patients) or via the access port of a Medtronic® pump previously surgically implanted for spasticity control (32 patients). Treatments were scheduled 8–11 weeks apart to facilitate patient compliance. A CBC with differential was obtained every 6 weeks following treatment to assess the level of hematological suppression. In addition, other laboratory tests such as liver function profiles and urinalysis were performed yearly or more frequently if clinically indicated.

Patients with a positive history of recurrent herpes infections were prophylactically treated with acyclovir for a 2 week period following ITMTX administration.

Patients were allowed to discontinue treatment at any point. After each treatment cycle, all adverse events were noted and further treatment only considered if there were no safety concerns. This treatment protocol was established prior to the chart review. Patients were followed for up to a total of eight treatment cycles and 1 year after their last treatment. At the time of their eighth treatment, 64 of 66 patients expressed the desire to continue receiving this therapy.

Patient assessment

EDSS

Patients underwent pre- and post-treatment neurological assessments, and Kurtzke expanded disability status scale (EDSS) evaluations. The nonblinded examining neurologist determined the EDSS scores of each patient at 1 year

prior to treatment commencement (pre-treatment), at the start of treatment (baseline), and after completion of eight treatment cycles or withdrawal (post-treatment).

Statistical analysis

Statistical analysis was performed using PASW Statistics software, version 18 (SPSS Inc., Chicago, IL, USA). EDSS data were treated as discrete ordinal scaled and analyzed by SPMS and PPMS group using the Wilcoxon signed rank test to determine the significance of treatment with ITMTX as a factor of patient EDSS score.

Adverse effects

All adverse events were recorded prior to each treatment cycle starting with the second treatment and at 1 year post final treatment. For repetitive complaints such as post-spinal headache, each occurrence was considered a separate event.

Protocol for discontinuation

ITMTX treatment was terminated at the physician's or patient's discretion. A full neurological evaluation and EDSS assessments took place if a patient discontinued treatment. The treating neurologist recorded any additional adverse effects of ITMTX treatment and discussed alternative treatment options. Discontinued patients' final treatment visit EDSS scores were used as post-treatment values if therapy was stopped before subjects completed eight cycles of treatment.

Results

ITMTX treatment and EDSS

Prior to treatment, all patients had active disease in some aspect (as detailed in the Methods). Nearly 90% of both PPMS and SPMS patients showed improvement or maintained a stable EDSS score between baseline and study completion (Table 2). One year prior to treatment, PPMS patients' mean EDSS score was 5.68 ± 0.70, and at baseline the mean EDSS score was 6.21 ± 0.77. After ITMTX therapy, the mean EDSS score for PPMS patients was 6.24 ± 0.87. The mean EDSS scores for SPMS patients prior to treatment, at baseline, and post-treatment reflect a similar slowed rate of progression: 5.82 ± 1.28, 6.15 ± 1.24, and 6.06 ± 1.32, respectively. Both PPMS and SPMS patients showed significant progression in EDSS scores prior to commencement of ITMTX therapy ($P < 0.001$ comparing baseline to pre-treatment EDSS for both patient groups).

Table 2 EDSS trends following ITMTX therapy

MS Type	Improving EDSS	Stable EDSS	Declining EDSS
PPMS	5 (15%)	23 (67%)	6 (18%)
SPMS	24 (28%)	53 (61%)	10 (11%)
Total	29 (24%)	76 (63%)	16 (13%)

Values reported as *n* (%)

PPMS primary progressive multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *EDSS* Kurtzke expanded disability status scale

Table 3 Effect of ITMTX therapy on Mean EDSS

MS type	Mean EDSS ± SD		
	1 year pre-treatment	Baseline at treatment start	Post-treatment (last or eighth treatment)
PPMS	5.68 ± 0.70	6.21 ± 0.77*	6.24 ± 0.87[†]
SPMS	5.82 ± 1.28	6.15 ± 1.24*	6.06 ± 1.32[‡]

PPMS primary progressive multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *EDSS* Kurtze expanded disability status scale

* $P < 0.001$ comparing baseline to pre-treatment EDSS

† $P = 0.642$ comparing post-treatment EDSS to baseline EDSS for PPMS patients

‡ $P = 0.014$ comparing post-treatment EDSS to baseline EDSS for SPMS patients

PPMS patients did not show a significant change between post-treatment and baseline EDSS ($P = 0.642$). After receiving ITMTX therapy, SPMS patients showed improvement in EDSS ($P = 0.014$) (Table 3).

Of patients whose disease was progressing as measured by the EDSS score in the year prior to receiving ITMTX, 66% stabilized, 17% continued to progress, and 17% showed improvement when post-treatment versus pre-treatment EDSS scores were compared (Table 4). Post-treatment positive effects on the EDSS were noted in patients who had stable EDSS scores in the year preceding treatment but had active disease as assessed by other parameters (relapses or increased MRI activity). In this group, improved EDSS scores were noted in 39% of patients, with 56% remaining stable, and only 5% with worsening EDSS.

Adverse events and reasons for discontinuation

Side effects from ITMTX treatment were minimal (Table 5). No adverse event required hospitalization. The most common complaints were transient fatigue (experienced by 29% of patients) and post-spinal headache (8.2% of patients). Two patients (1.7%) experienced clinically

Table 4 Disease progression as measured by EDSS following ITMTX therapy

Pre-treatment status	Post-treatment status	EDSS 1 year Pre-treatment	EDSS baseline at treatment start	EDSS post-treatment
Stable $n = 41$	Stable $n = 23$	6.28 ± 1.06	6.28 ± 1.06	6.28 ± 1.06
	Declining $n = 2$	7.25 ± 1.77	7.25 ± 1.77	7.75 ± 1.77
	Improving $n = 16$	6.06 ± 1.64	6.06 ± 1.64	5.50 ± 1.66
Declining $n = 76$	Stable $n = 50$	5.71 ± 0.93	6.34 ± 0.91	6.34 ± 0.91
	Declining $n = 13$	5.69 ± 0.78	6.31 ± 0.75	6.85 ± 0.72
	Improving $n = 13$	4.92 ± 0.91	5.62 ± 0.98	5.12 ± 0.98
Improving $n = 4$	Stable $n = 3$	4.67 ± 1.26	4.17 ± 1.26	4.17 ± 1.26
	Declining $n = 1$	6.0	5.5	6.5

Table 5 Adverse events

Adverse event	*n*
Fatigue	36
Headache	10
Leukopenia	2
Vomiting	1
Paresthesia	2
Concomitant infection	5
Total	56

Table 6 Reasons for discontinuation

Reason	*n*
Perceived lack of effect	28 (51%)
Hold was more than 4 months	15 (27%)
Travel distance was too great	4 (7.3%)
LP headache	2 (3.6%)
Fatigue	1 (1.8%)
Concomitant unrelated condition	2 (3.6%)
Death	3 (5.5%)[a]
Total	55

[a] All patients died of unrelated causes: coronary artery disease, pulmonary embolism, disability/aspiration

insignificant leukopenia. Concomitant infections caused five patients (4.1%) to be placed on treatment hold: one patient with candidiasis was treated with a topical antifungal cream, one patient with chronic venous stasis dermatitis developed secondary cellulitis, one patient developed a decubitus ulcer, and two patients presented with active symptoms of urinary tract infection (UTI) on the day of their scheduled ITMTX therapy.

In total 55 patients discontinued ITMTX therapy (Table 6). The majority of patients who discontinued ITMTX therapy requested to terminate because of a perceived lack of effect ($n = 28$). Also, 15 patients discontinued because they were put on ITMTX hold which exceeded more than 4 months. A hold was put in place if the patient missed an appointment, was considering stopping treatment, or had an unrelated active infection such as UTI. Any hold because of infection was evaluated and each was determined to be unrelated. No cases of meningial infection occurred, and none of the hold infections were considered serious, as no hospital admissions were necessary and all hold infections resolved within a few days after starting antibiotic treatment or antifungal/viral agents. These patients, who were put on hold, did continue ITMTX therapy after their hold, but for study purposes were counted as early discontinuation because of an extensive time between ITMTX treatments. Only one patient stopped ITMTX treatment due to fatigue. Three deaths were reported in the study population. A 74-year-old woman died of coronary artery disease (at treatment commencement, ischemic heart disease in this patient had not been investigated). A 58-year-old woman died of a pulmonary embolism. A 62-year-old woman died from aspiration pneumonia as a result of her profound MS-related disability. None of these deaths were causally related to ITMTX therapy.

Discussion

This study is a retrospective analysis of patients receiving intrathecal methotrexate for treatment-unresponsive MS at our center. We report that ITMTX is remarkably well tolerated and that there were no cases of significant morbidity or mortality attributable to the treatment. The efficacy trends are encouraging, as 89% of patients with SPMS and 82% of patients with PPMS stabilized or showed improvement in EDSS scores. Both patient groups showed significant decline in EDSS pre-treatment to baseline; while PPMS results show no statistically significant difference in EDSS scores from baseline to post-treatment, accepting the null hypothesis in this case actually suggests progression slowed. As SPMS patients showed significant improvement in EDSS scores, it is possible that a larger sample of PPMS patients might have shown slowed progression actually trending to improvement. It should be noted that there was no significant difference in clinical response to therapy or adverse events between patients who received treatment through lumbar puncture versus the access port of a Medtronic® pump. In a subset of patients, brain MRI findings also supported the clinically positive trends, with stabilization of MRI in both PPMS and SPMS patients (supplementary material, Appendix A).

There were major concerns about safety when ITMTX was considered for use in MS. These included the occurrence of treatment-associated leukoencephalopathy, opportunistic CNS infections, and the constitutional effects (such as nausea and vomiting) of using an intrathecal chemotherapeutic agent. In addition, we selected patients with considerable disability (68% of patients with EDSS $\geq$ 6.0) who are more susceptible to treatment complications related to immunosuppression because of their propensity to have associated conditions such as skin breakdown and urinary tract infections. Despite these concerns, the use of ITMTX in these patients did not result in any serious treatment complications, and in no patient could neurological worsening be directly attributed to the treatment. About 65% of patients reported no adverse effects despite multiple courses of treatment, and only 3 of 121 patients discontinued therapy because of treatment intolerance.

There are a variety of therapeutic options that are FDA-approved for the treatment of MS. However, only mitoxantrone is approved for progressive forms of MS, and its use is limited because of cardiac toxicity and its association with leukemia [14, 22]. Furthermore, mitoxantrone may not have any beneficial effect on the non-relapsing form of SPMS and is ineffective in PPMS. Many of the newer agents under consideration for use in MS, such as rituximab [15, 16], fumarate [8], alemtuzumab [1, 5], and cladribine [20], are all either ineffective in progressive forms of MS or are being investigated only in RRMS. There is currently a trial underway for fingolimod [11] in PPMS, but no preliminary results have been presented. A review on the lack of treatment options for PPMS was recently published and emphasizes the dire need for finding efficacious treatment for patients with PPMS [13]. Even the most radical current treatment of autologous hematopoietic stem cell transplantation following bone marrow ablation is highly effective in early inflammatory MS, while earlier trials with progressive forms of MS did not have positive outcomes [7]. Thus, there is a real therapeutic vacuum in non-relapsing SPMS and in all forms of PPMS. The use of ITMTX in this unblinded, uncontrolled, retrospective analysis does provide a basis for further investigation of this agent in progressive disease.

The possible mechanism of action of ITMTX merits some discussion. Chemotherapeutic immunosuppressive agents have been extensively investigated in MS, but have limited efficacy in progressive forms of MS. This suggests that profound peripheral depletion of lymphocytes as a therapeutic strategy, while highly effective in RRMS and inflammatory (relapsing) forms of SPMS, has little or no benefit in late stage SPMS or PPMS. This may be because these progressive forms of MS are pathologically in a degenerative and non-inflammatory phase of the disease and are, therefore, unresponsive to lymphocyte depletion. One of the pathologic hallmarks of the chronic stage of disease is glial proliferation and scarring [9, 24], and it is possible that ITMTX retards this aspect of the disease. In support of this hypothesis, preliminary ongoing studies show that addition of MTX to neural cell cultures selectively inhibits astroglial proliferation [25]. An alternate explanation for the efficacy trends seen with ITMTX may be that some of the immune abnormalities seen in MS are primarily CNS in origin and are, therefore, more responsive to intrathecal therapy. There is accumulating evidence that in a proportion of MS patients, there are follicular structures in the meninges and Virchow-Robin spaces [10, 26], and these follicles enriched in lymphocytes and dendritic cells may drive a CNS autologous autoimmune response [18]. This CNS restricted immune response may be unaffected by systemic immunosuppression, or by agents such as natalizumab that stop lymphocyte trafficking across the blood brain barrier. It is possible that ITMTX acts by inhibiting the autoimmune activity generated by these meningial follicles. This could be investigated further by determining the effects of ITMTX on CSF chemokine levels (such as CxCL-13) that may be produced by follicular lymphocytes.

ITMTX was used at our center as an off-label, inexpensive (medication costing approximately $2 USD plus the cost of the lumbar puncture) treatment for disabled patients with MS, who had no alternative therapeutic options, in an attempt to modify the otherwise dismal

course of progressive disease. Analysis of the natural history of MS patients shows that the risk of sustained progression (an increase of EDSS score by 1 point) was 50% by 7 years and 70% by 15 years [7]. The likelihood of progression is also affected by baseline EDSS score, with scores of 4.0–5.5 being more at risk for progression than scores of 3.0–3.5 [7]. After initiation of ITMTX and as part of the routine clinical follow-up, it became evident that this treatment appeared remarkably well-tolerated and that, anecdotally, patients perceived improvement or stability. Using a nonvalidated quality of life scale, more than half of patients reported improved quality of life, and only 12% of patients reported worsened quality of life during ITMTX therapy (data not shown).

The use of ITMTX has not previously been reported in MS. Despite this study's shortcoming of being uncontrolled and unblinded, it is our opinion that our positive experience with ITMTX in a relatively large number of patients should be reported. Furthermore, the patients at study entry were significantly disabled (mean baseline EDSS 6.17), and at present there are no viable therapeutic options for this study population. In conclusion, the findings support the need for a robust, prospective, and controlled clinical trial of ITMTX in patients with PPMS and in non-relapsing SPMS.

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