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Full Length Research Paper

The Effects of Herbal-Marine Compound MS14 on Quality of Life in Multiple Sclerosis: A Randomized Placebo-Controlled Crossover Trial

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Current research into new drugs is focused on agents that will change multiple sclerosis process. MS_{14} is an herbal-marine product, based on anecdotal evidences in traditional Iranian medicine (TIM). The objective of this study was to assess the safety and efficacy of MS_{14} in volunteer patients. This study was a randomized placebo -controlled, double blind, crossover clinical trial in patients who had not responded to common MS drug regimens. Common toxicity criteria and quality of life (QOL) ques-tionnaire were assessed. No significant changes were observed in vital signs, biochemical, hema-tological, liver and kidney function tests. Moreover, the improvement of patients' mobility (lower limb) was significant, comparison before treatment and placebo group (p-value: 0.048). These results suggest the potential benefits of MS_{14} on QOL in patients and attenuating and remodeling of multiple sclerosis disease and although the results confirm the safety and relative efficacy of MS_{14}.

Key words: Multiple sclerosis, MS_{14}, Iranian traditional medicine.

INTRODUCTION

Multiple sclerosis (MS) is characterized by a relapsing remitting or progressive course and a pathologic triad of CNS inflammation, demyelination and gliosis (Braunwald and Fauci, 2005). MS affects thousands of sufferers worldwide and in many cases it is characterized by the relentless progression of the disease with increasing dis-ability. According to recent investigations, treatment with interferon or other disease modifying drugs (DMDs) has limited benefit and some side effects. Furthermore the progression of disease is not much affected by these drugs (Braunwald and Fauci, 2005; Galetta and Markowitz, 2005; Coyl and Hammad, 2003). So there is a need for newer therapeutics or neuroprotective agents in treatment of MS.

MS_{14} is an Iranian herbal-marine compound that has been patented by invention and patent registration office of Islamic republic of Iran (no: 29350) and classified as equivalent to food with no observable adverse effect level (NOAEL) (Hajhashemi et al., 2004; Klaassen, 2001). According to analytic data this compound contains many inorganic salts or complexes and also trace elements such as bromine (Br), strontium (Sr), vanadium (V), tita-nium (Ti), nickel (Ni) and zinc (Zn) (Ahmadi, 2004). One study strongly suggests that MS_{14} has a protective action against preoperative damage to biomembranes and intro-duces it as an antioxidant agent (Naderi et al., 2004, un-published). Sub-acute toxicity study in rats confirms the

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safety of MS_{14} (clinical, histopathological, hematological and in blood biochemistry) (Hajhashemi et al., 2004). Anecdotal bits of evidence rooted in Iranian traditional medicine suggest that MS_{14} could help MS patients and in practice of this system of complementary and alter-native medicine, it has been shown to be beneficial in certain multiple sclerosis patients. In the study of MS_{14} in EAE model (experimental allergic encephalomyelitis) have shown that oral treatment of the EAE mice with MS_{14} not only halts the progression of the disease but also attenuates the inflammation in CNS indicating that this herbal-marine compound has anti-inflammatory eff-ects (Tafreshi et al., 2008) . A small pilot clinical trial on volunteer MS patients also indicated that MS_{14} may have some benefits on quality of life (QOL) and some symptoms of the patients (Gharegozli, 2004; unpublished data, Department of Neurology, Shahid Beheshty University of medical science). After some reports from minor pilot studies on volunteer patients suffering from MS which indicated the usefulness of MS_{14}, it is incumbent upon us to investigate this drug, for it offers the potential of an oral therapy for MS with few side effects.

Overall, alleviation of clinical and neurological symptoms in EAE mice by MS_{14} explained the beneficial eff-ects of traditionally used MS_{14} in MS patients. With the above information at hand, upon receiving the required permit from the respective medical ethics committee, we performed a randomized placebo-controlled crossover study with MS_{14} on multiple sclerosis patients with cerebellar ataxia who had not responded to common MS drug regimens, to assess the safety and efficacy of MS_{14}.

MATERIALS AND METHODS

Patients

We included MS patients aged at least 18 years, with relapsing-remitting or secondary progressive form of multiple sclerosis accor-ding to the McDonald criteria (Diagnostic McDonald Criteria for Multiple Sclerosis, 2008). Patients selected were not to be in an acute attack by at least one month prior to start of the study. They were to demonstrate cerebellar symptoms such as dysmetria or ataxic tremor or gait and no concurrent natural or herbal treatment should have been taken by them.

Exclusion criteria consisted of presence of cardiovascular diseases, pregnancy or breast feeding, relapse during the previous 1 month or during the study, active infectious disease, introduction of new treatments for MS during the previous month, concurrent pharmaceutical drugs for cerebellar ataxia, severe cognitive or psychotic disorder and major disturbance in blood factors (bio-chemistry and hematology) in primary lab data.

Written informed consent was obtained from the patients before enrollment. The study protocol was approved by research ethics committee of Shahid Beheshti University of medical sciences. The study was conducted according declaration of Helsinki.

Intervention

We used the Poison method for assigning patient to randomly receive either active treatment (D) or placebo (P) as they enter the study, in the 2 phases. In the first phase, patients in group A started with MS_{14} (50 mg/kg/day as 500 mg oral caplets divided to 3 doses), being on active medication for 3 weeks before starting placebo and patients in group B started with placebo caplets for 3 weeks. In the second phase, which took place after a 1 month washout period to avoid the fluctuation of clinical examination, the groups were crossed over: group A received placebo group B received MS_{14} for 3 weeks. All patients, staff involved in adminis-tration of the interventions and those assessing the outcomes were blinded by irrelevant supervisor.

Clinical and paraclinical assessments

Each patient was evaluated at the first visit and the end of each phase for common toxicity criteria (CTC V.2) (National Cancer Insti-tute, 2003) and clinical signs and symptoms of MS. CTC included vital signs, liver function, kidney function and urinary, blood and bio-chemistry tests (Table 1 and 2). Treatment response rate was eva-luated in accordance with Hamburg quality of life questionnaire on multiple sclerosis (HAQUAMS) (Gold et al., 2001) and classified to 7 groups including sensory, cognitive and fatigue, upper extremity mobility, lower extremity mobility, urination, defecation, sexuality, communication and mood.

Statistical analysis

All statistical analyses were performed by means of SPSS software (version: 15.0). The assumption of normality was assessed using the Kolmogorov-Smirnov test. P-values less than 0.05 were consi-dered as statistically significant. This crossover study was per-formed and analyzed based on the methods described in the Pocock clinical trial (Pocock, 1991). Groups were assigned the letter “i” (1 = DP and 2 = PD) where “D” represents drug and “P” re-presents placebo; the time phases were assigned the letter “j” (1 or 2). For each variable tested, D was calculated and corresponded to the post-treatment value minus pre-treatment value for group during phase . X denotes the post-treatment value for group in the phase . This way, the carry-over effect was tested by com-paring $D_{11} + D_{12}$ with $D_{21} + D_{22}$ and treatment effect was assessed by comparing $X_{11} - X_{12}$ with $X_{21} - X_{22}$ when there was no evidence of carry-over effect. Statistical evaluation was performed using Mann-Whitney test and the paired Wilcoxon rank sum test.

RESULTS

Patients’ characteristics

38 patients (31 women and 7 men) were included in this study; 20 were randomly assigned to group A and the rest comprised group B. The mean age of participants was 30.8 years (range 18 to 56). At the time of the study, patients were receiving 1 or more of the following treat-ments: interferon-beta (1a or 1b), cyclophosphamide, or methotrexate.

Treatment response

No adverse effects were seen in administration of MS_{14} with respect to common toxicity criteria in any of the patients studied (Table 1 and 2). A subjective effect on fatigue and cognitive signs was frequently observed with either placebo or MS_{14}. Treatment with placebo and treat-ment with MS_{14} both improved the evaluation parameters,

Table 1. Analyzed results of common toxicity criteria evaluation.

Parameters	Differences (treatment effect) [a]			Sums (interaction) [b]		
	Group A (MS14 /Placebo)	Group B (Placebo/ MS14)	P-value	Group A (MS14 /Placebo)	Group B (Placebo/ MS14)	P-value
Red Blood Cell (RBC)	0.8 (0.31)	-0.03 (0.10)	0.399	9.26 (0.60)	9.13(0/60)	0.815
Hemoglobin	0.68(2.66)	-0.014 (0.43)	0.735	24.95 (3.88)	26.50(1/98)	0.000
Hematocrit	0.80(2.94)	0.29 (2.39)	0.966	80.53 (8.81)	82.37(7/39)	0.271
White Blood Cell (WBC)	-2.23 (5.72)	-3.23 (7.06)	0.767	13.43 (5.89)	16.20(8/64)	0.422
Platelet	18.25(65.26)	-3.83 (35.31)	0.512	513/92 (129.52)	435.17(57/34)	0.472
Erythrocyte Sedimentation Rate (ESR)	1.00(7.18)	-0.67 (7.10)	0.962	25.16 (17.74)	22.33(23.83)	0.190
C-Reactive phase Protein (CRP)	0.23(0.83)	0.01 (0.02)	0.497	0.24 (0.82)	0.01 (0.01	0.373
Sodium (Na)	-0.92 (5.30)	0.92 (5.30)	0.876	280.92 (5.50)	278.00 (5.31)	0.152
Potassium (K)	0.20(0.58)	-0.35 (0.39)	0.036 [c]	8.62 (0.56)	8.25(0.52)	0.131
Calcium (Ca)	0.37(0.40)	0.06 (0.82)	0.445	19.07 (0.88)	18.94(0.73)	0.611
SGOT	1.83 (15.40)	4.50 (6.56)	0.534	44.33 (15.13)	40.25(10.22)	0.536
SGPT	3.50 (16.52)	-0.75 (10.29)	0.374	48.50 (22.22)	38.75(15.90)	0.396
Blood Urea Nitrogen (BUN)	-1.72 (8.03)	0.29 (4.3)	0.555	43.8 (12.53)	42.86(11.51)	0.964
Creatinine (Cr)	-0.19 (0.22)	-0.15 (0.10)	0.918	1.57 (0.25)	1.51(0.42)	0.479
Urine Analysis	0.33(1.36)	0.43 (0.53)	0.213	1.00 (1.26)	1.00(0.82)	0.822

(a) Differences X1–X2: post treatment value for period 1 minus post treatment value for phase.
(b) Sums D1 + D2 where Di designs the post treatment value minus pre treatment value for the phase i (i = placebo or MS_{14}).
(c) Significant interaction effect.

yet, a subjective effect on lower limb motion was obser-ved only with MS_{14} as indicated in Table 3.

DISCUSSIONS

Significant advances in the treatment of MS have been seen in recent years, but further improvements in therapy are required as all patients do not respond optimally. An approach to enhancing MS treatment is to combine drugs that impact on different aspects of the disease process. Currently, it is increasingly being recognized that com-bination therapy with existing or novel MS therapeutics may produce a more favorable clinical outcome than monotherapy in the disease and therefore represent the future of MS treatment (Pattia et al., 2004; Giuliania et al., 2005).

The use of complementary and alternative medicine (CAM) and dietary supplements appears to be high amongst the general population for different ailments, and in patients with MS (Hunly and Ernest, 2000; Pucci et al., 2004; Stuifbergen and Harrison, 2003; Simile and Hardy, 2002; Nayak et al., 2003). Because these approa-ches are not definitely effective, they may be of limited interest to physicians and other conventional health provi-ders. In contrast, for patients with MS these interventions may be of considerable interest because they may be mildly effective yet significantly inexpensive and relatively safe. Vitamin D, ginkgo biloba, cannabinoids, and Padma 28 produce immunomodulatory actions and therapeutic effects in experimental autoimmune encephalomyelitis (Hunly and Ernest, 2000; Pucci et al., 2004; Stuifbergen and Harrison, 2003; Simile and Hardy, 2002; Nayak et al., 2003). For these compounds, however, there is not enough clinical trial data or safety information to support their use as disease modifying therapies (Hunly and Ernest, 2000; Pucci et al., 2004; Stuifbergen and Harrison, 2003; Simile and Hardy, 2002; Nayak et al., 2003).

In our exploration of complementary and alternative medicine, we are of the following belief that great assets as therapeutic facts lay within different schools of tradi-tional medicine; schools of therapeutics which stood the test of time as seen in 5 thousand years old tradition of Chinese traditional medicine or 8 thousand years old tradition of Iranian traditional medicine. We further beli-eve that the knowledge which lies in the schools of tradi-tional medicine (ethno-medicine), if efficiently used, may lead to novel drug discovery and development through shortened explorative paths based on a reverse pharmacology path (Patwardhan

Table 2. Results of vital signs evaluation in patients, no statistically significant difference was observed.

Placebo		Treatment		Control		Vital signs
S.D	Mean	S.D	Mean	S.D	Mean	
7.67	110.15	8.55	109	11.36	112.89	Systolic Blood Pressure
8.1	78.9	8.14	76.83	8.43	77.73	Diastolic Blood Pressure
5.85	81.87	8.55	82.1	20.19	84.89	Pulse Rate
1.41	12.28	1.66	12.2	10.59	14	Respiratory Rate
0.02	39.92	0.02	36.9	0.15	36.87	Temperature

Table 3. Treatment response rate according to Hamburg quality of life questionnaire in multiple sclerosis (HAQUAMS), analyzed by Wilcoxon test.

Groups / Problem	MS_{14} (Pretreatment)	Placebo (Pretreatment)	MS_{14} / Placebo
Sensory	0.436	0.678	0.569
Fatigue and Cognitive	0.036*	0.034*	0.917
Upper Limb motion	0.230	0.752	0.146
Lower Limb motion	0.063*	0.191	0.048*
Urination, Defecations and Sexuality	0.215	1	0.831
Communication	0.357	0.701	0.450
Mood	0.332	0.032	0.584

(*) P-value < 0.05

et al., 2004; Fabricant, 2001). The instance of the use of cannabinoids in the treatment of MS is one such example. Cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale, but they were able to a degree to unmask objective improve-ment in mobility and augmented the patients' feelings of an improvement in pain (Zajicek et al., 2003). This sug-gested that cannabinoids may be clinically useful in the treatment of MS (Zajicek et al., 2003) and a standardized *Cannabis sativa* plant extract might lower spasm fre-quency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs (Vaney et al., 2004).

MS_{14} is an herbal-marine compound which has been recognized as a remedy in the treatment of MS based on available data within the libraries on CAM. MS_{14} ameliorates experimental allergic encephalomyelitis (Tafreshi et al., 2008) but our data is subjective and we do not know the mechanisms by which MS_{14} acts on multiple sclerosis disease. The results of this study confirm the relative safety of this remedy in human but objective studies are required to confirm the efficacy of this natural agent. The present study further demonstrates that MS_{14} can improve the lower limb mobility which may be due to multiple mechanisms that need to be further investigated.

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