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Cognitive dysfunction in patients with multiple sclerosis treated with different types of interferon beta: A randomized clinical trial

Naghmeh Mokhber [a,1], Amir Azarpazhooh [b,c,d,1], Elias Orouji [e], Stephen M. Rao [f], Bita Khorram [g], Mohammad Ali Sahraian [h], Mohsen Foroghipoor [e], Morteza Modares Gharavi [i], Sorayya Kakhi [j], Karim Nikkhah [e,*], Mahmoud Reza Azarpazhooh [e]

[a] Department of Psychiatry, Avicenna Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Biological and Diagnostic Sciences, Faculty of Dentistry, University of Toronto, Canada
[c] Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Canada
[d] Toronto Health Economics and Technology Assessment Collaborative, University of Toronto, Canada
[e] Department of Neurology, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Neurological Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[g] Toronto, Canada
[h] Department of Neurology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
[i] Department of Psychology, Avicenna Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[j] Mashhad University of Medical Sciences, Mashhad, Iran

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic autoimmune disease that can deteriorate cognitive function in at least 50% of patients even in the early stages.
Objective: We conducted a three-arm parallel study with balanced randomization to evaluate the effect of various disease-modifying therapies (DMTs) on cognitive function in MS.
Methods: Ninety newly diagnosed, definite MS subjects referred to Ghaem Medical Center, Mashhad, Iran, were enrolled into this study between 2006 and 2009. They were randomly categorized into three DMT groups; Avonex, Rebif and Betaferon. Cognition status was assessed in MS patients at baseline and 12 months after treatment with DMTs using the 5 tests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N).
Results: The Symbol Digit Modalities Test scores improved in all groups at 12 month vs. baseline (Avonex: 34.50 vs. 38.95, $p = 0.011$; Rebif: 35.30 vs. 40.13, $p = 0.001$; Betaferon: 26.18 vs. 29.32, $p = 0.029$). The Selective Reminding Test (SRT)-Total, the 10/36-Delay, and the Paced Auditory Serial Addition Test-Easy were improved in Avonex and Rebif but not in Betaferon group. The SRT-Delay and Word List Generation were improved only in the Avonex group. There was no significant difference in other components of the BRB-N among these three treatment groups.
Conclusions: Different types of DMTs may improve some aspects of cognitive function in patients with MS. Treatment with Avonex and Rebif (Interferon beta-1a preparations) were more helpful in resolving the cognitive impairments in MS patients compared to Betaferon (Interferon beta-1b) as investigated in this study.

1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease that affects at least 2.5 million people worldwide [1]. Traditionally, MS is defined as recurrent exacerbations due to central nervous system (CNS) involvement, which leads to physical disability. However, MS can also deteriorate cognitive function even in the early stages [2]. The frequency of cognitive dysfunction was formerly underestimated. Recent studies have shown that at least half of MS patients will develop cognitive dysfunction, which can significantly influence their daily functional skills [3–5]. By improving cognitive evaluation techniques, it has been possible to identify mild and early changes in cognitive functions as well as specific aspects such as memory, attention, visual–spatial abilities, executive functions, and processing speed in MS [6–11]. For this purpose, the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) [12] was constructed to test different domains of cognition which are frequently impaired in MS [13–17].

This group of tests explores most of the cognitive functions while minimizing the overlap between them [18–21]. The BRB-N is sensitive to early cognitive impairment in patients with MS [22–24] and several studies have consistently indicated that MS patients perform significantly worse than controls on this test [25,26]. The cognitive dysfunction may be related to lesion burden, brain atrophy, and physical disability [27,28]. However, the exact mechanism remains a matter of debate.

* Corresponding author. Tel.: +98 511 606 7489; fax: +98 511 842 9828.
E-mail address: NikkhahK@mums.ac.ir (K. Nikkhah).
[1] These authors contributed equally to the paper.

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In spite of the correlation between cognitive dysfunction and MS, there are still limited data considering the management of the developed dysfunction. Treatment is crucial since it can improve the functional level of daily activities and quality of life. During the past decade, several disease-modifying therapies (DMTs) have become available for the treatment of MS and have altered the long-term course of the disease [29]. These agents are generally safe and well tolerated, can reduce the risk of physical disability, and can diminish the number of active brain lesions visible on magnetic resonance imaging images [30]. It is believed that treatment with interferon beta-1a exerts its neuropsychological effects via both short-term mechanisms by inhibiting inflammation, and also long-term mechanisms by slowing or preventing further CNS tissue damage [31]. However, very few studies have examined the effect of treatment on cognition.

Several clinical trials have shown beneficial effects of DMTs on long-term cognitive measures which may even reduce cognitive deficits in MS patients [22–24,32–35]. Animal models of MS, along with assessments of the clinical response to DMTs, suggest the disease is mediated immunologically [36]. The immune system effects of Interferon beta, relevant to its therapeutic mechanisms in MS, are not well understood but are believed to include decrease in T-cell activation, induction of cytokine shifts in favor of an anti-inflammatory effect, prevention of T-cell adhesion and extravasation across the blood brain barrier, as well as induction of T-regulatory cells [37]. Besides such anti-inflammatory actions, MS-related changes in cortical matter play a critical role in the development of cognitive symptoms [38] and since interferon beta can decrease the volume of brain lesion [39], it can have a protective effect against cognitive decline.

Given the high incidence and the importance of cognitive dysfunction in MS, we designed this clinical trial to evaluate, using the BRB-N, the effect of various DMTs on the cognitive function of patients with MS. We hypothesized that although all DMTs have positive effects on cognition in MS patients, various preparations of Interferon beta treatment could improve the cognitive status in these patients at different levels.

2. Method

2.1. Trial design and protocol

This study is a double blind three-arm parallel study, with balanced randomization conducted in the Department of Neurology, Mashhad University of Medical Sciences, Mashhad, Iran, between May 2006 and June 2009. The flow of the study is presented in Fig. 1.

All subjects gave their consent to the study in accordance with the informed consent regulations of the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (protocol number: 84393-1). Eligible participants were all new cases of definite MS according to the revised McDonald criteria, which include magnetic resonance imaging, detailed neurological history and examination, and paraclinical laboratory tests of cerebrospinal fluid findings and visual-evoked potential [40]. Patients were excluded if they had a history of substance abuse or prior treatment with any type of DMTs. Patients were also excluded if they showed any signs of depression. For this purpose, the study neuropsychiatrist performed semi-structural psychiatric interviews using the Beck Depression Inventory to assess symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and decrease in libido [41].

The study neurologist (MRA) enrolled the participants and allocated the subjects using a computer-generated list of random numbers to the 3 treatment groups of three distinct commercially available forms of interferon beta. Avonex was administered 30 mcg once per week via intramuscular injection; Rebif was administered 44 mcg three times per week via subcutaneous injection; and Betaferon was administered 0.25 mg every other day via subcutaneous injection. Injections were

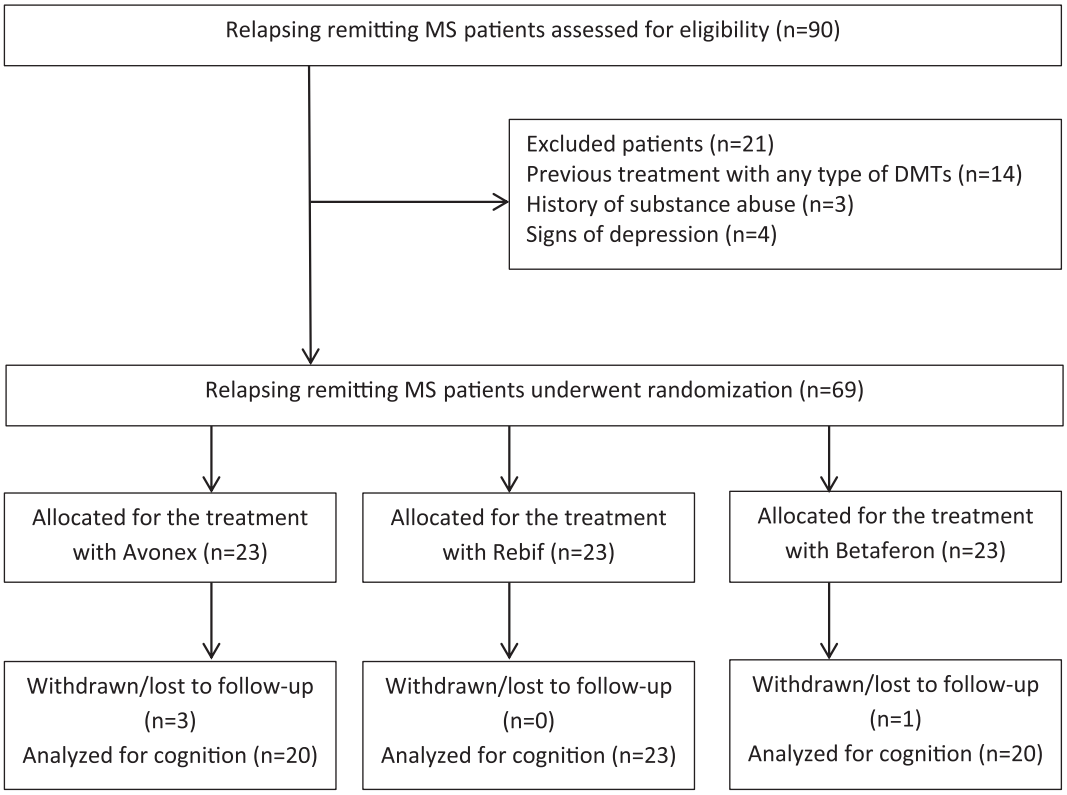

Fig. 1. Flow diagram of the three-arm parallel study to investigate cognition in MS patients.

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