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Efficacy and safety profile of memantine in patients with cognitive impairment in multiple sclerosis: A randomized, placebo-controlled study

Laure Peyro Saint Paul [a,*], Christian Creveuil [a], Olivier Heinzlef [b], Jerome De Seze [c], Patrick Vermersch [d], Giovanni Castelnovo [e], Philippe Cabre [f], Marc Debouverie [g], Bruno Brochet [h], Benoit Dupuy [i], Pierre Lebiez [i], Éric Sartori [j], Pierre Clavelou [k], David Brassat [l], Christine Lebrun-Frenay [m], David Daplaud [n], Jean Pelletier [o], Irène Coman [p], Patrick Hautecoeur [q], Ayman Tourbah [r], Gilles Defer [s,t]

[a] Department of Biostatistics and Clinical Research, Centre Hospitalier Universitaire de Caen, France
[b] Department of Neurology, Centre Hospitalier de Poissy, France
[c] Department of Neurology, Centre Hospitalier Régional et Universitaire de Strasbourg, France
[d] Department of Neurology, Centre Hospitalier Régional et Universitaire de Lille, France
[e] Department of Neurology, Centre Hospitalier Universitaire de Nîmes, France
[f] Department of Neurology, Centre Hospitalier de Fort-de-France, France
[g] Department of Neurology, Centre Hospitalier Universitaire de Nancy, France
[h] Department of Neurology, Centre Hospitalier Universitaire de Bordeaux, France
[i] Department of Neurology, Centre Hospitalier de Cherbourg, France
[j] Department of Neurology, Centre Hospitalier de Lorient, France
[k] Department of Neurology, Centre Hospitalier Universitaire de Clermont-Ferrand, France
[l] Department of Neurology, Centre Hospitalier Universitaire de Toulouse, France
[m] Department of Neurology, Centre Hospitalier Universitaire de Nice, France
[n] Department of Neurology, Centre Hospitalier Universitaire de Nantes, France
[o] Department of Neurology, Assistance Publique des Hôpitaux de Marseille, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Marseille, France
[p] Department of Neurology, Assistance Publique des Hôpitaux de Paris, France
[q] Department of Neurology, Groupement des Hôpitaux de l'Institut Catholique de Lille, France
[r] Department of Neurology, Centre Hospitalier Universitaire de Reims, France
[s] Department of Neurology, Centre Hospitalier Universitaire de Caen, France
[t] INSERM U 919, GIP Cyceron, Caen, France

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ABSTRACT

Memantine, an uncompetitive antagonist of N-methyl-D-aspartate (NMDA)-type glutamate receptors that was approved for the treatment of moderate to severe Alzheimer's disease, has been negatively evaluated for the treatment of cognitive disorders of multiple sclerosis, but these studies were conducted only during short-term administration and on a heterogeneous group of patients with different forms of the disease. In addition, many adverse reactions were observed in these patients.

Aims: The purpose of the "EMERITE" (NCT01074619) study was to examine the efficacy and safety of the long-term administration of memantine as a symptomatic treatment for cognitive disorders in patients with relapsing-remitting multiple sclerosis (RR-MS).

Methods: The study was supported by the French Ministry of Health and received additional support from Lundbeck. In this double-blind, placebo-controlled, parallel group, randomized trial, the participants were assigned to receive memantine (20 mg/day) or a placebo for 52 weeks. The participants included males and females, 18–60 years of age, with a diagnosis of RR-MS and presenting with a cognitive complaint and/or demonstrating moderate cognitive impairment. The data were collected in the Department of Neurology in 19 French centers. The primary outcome was the Paced Auditory Serial Addition Test (PASAT) score at week 52. Secondary measurements included additional neuropsychological tests and the annualized relapse rate. The scores were adjusted according to the baseline scores in the analysis. The safety was assessed by the number of adverse events. The random sequence was generated using the Excel software. At each center, only the pharmacist had access to the allocation sequence and could be asked to unblind the trial.

Results: Fifty patients were allocated to the memantine group, and 43 to the placebo group. The intent-to-treat

* Corresponding author at: Cellule de Promotion de la Recherche Clinique, Bureau 03-810, CHU de CAEN, Avenue de la Côte de Nacre, 14033 Caen cedex, France.

(ITT) population included 31 patients in each group. After adjusting for the PASAT scores at baseline, the PASAT scores at the end point did not differ between the memantine and the placebo groups ($p = 0.88$). Adjusted mean score difference (memantine minus placebo), was −0.40 (95% confidence interval: -5.5; +4.7). No significant differences were observed for the secondary outcomes (short term memory and attention scores, EDSS, and relapse rate). The findings remained unchanged after multiple imputation of the missing values. Neurological and psychiatric adverse events were significantly higher in the memantine group than in the placebo group, and these parameters were higher than those reported in the product literature of memantine.
Conclusions: No differences between the placebo and memantine groups were observed. Nevertheless, the tolerability of memantine was significantly worse than expected.

1. Introduction

Cognitive impairment is frequently observed in multiple sclerosis (MS) patients and can significantly disrupt day-to-day activities, social relationships, or the ability to work in severe cases [1, 2]. Currently, no evidence exists for a drug therapy that promotes sustained improvement of cognitive impairment in these patients [3–5].

Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved for the treatment of moderate to severe Alzheimer's disease (AD) because this drug has been shown to improve cognitive dysfunction in patients with AD [6, 7]. However, memantine shows limited clinical effects over the short term for some AD patients and exhibits potentially under-recognized toxicity over the long term [8, 9].

The rationale for using memantine as a symptomatic therapy for cognitive dysfunction in MS patients reflects the fact that this drug improves the cognitive symptoms of AD, and the glutamatergic system has been implicated in the pathophysiology of MS, as increasing data suggest a potential role for NMDA receptors in both neurodegenerative and inflammatory processes [10–12]. Indeed, the pharmacological inhibition of NMDA glutamate receptors via memantine has reduced the severity of experimental autoimmune encephalomyelitis (EAE) in rats and protected retinal ganglion cells from apoptosis in an experimental autoimmune optic neuritis model [13–15]. In addition, in vivo evidence of impaired brain glutamate homeostasis, which is associated with lower cognitive performance, has recently been obtained in MS patients [12, 16]. Consequently, the glutamate system and NMDA receptors have become attractive targets for drug development for MS (including cognitive dysfunction).

Two previous studies using memantine have not demonstrated improved cognitive performance in MS patients. The first study [17] was discontinued after a small number of subjects were enrolled due to adverse reactions. The second study [18] was only conducted for 16 weeks and included all types of MS patients, which limited the chance of observing the potential cognitive effects of memantine due to the heterogeneous population and short-term drug exposure.

We initiated a similar randomized, placebo-controlled study to examine the efficacy and safety of memantine during long-term administration (52 weeks) in moderately impaired, non-demented, relapsing-remitting multiple sclerosis patients (RR-MS). The primary objective of the present study was to show an improvement in working memory and sustained attention, measured using the Paced Auditory Serial Addition Test (PASAT) score. The secondary objectives focused on attentional performance, short term memory, and clinical disability.

2. Design and research plan

2.1. Standard protocol approvals, registration, and patient consent

The trial was registered at www.clinicaltrials.org (NCT01074619) and was approved by the Regional Ethical Standards Committee on Human Experimentation (France, CPP NOIII 2004-28). The official title was "EMERITE: **E**ffects of **ME**mantine on cognitive disorders of **R**elapsing-rem**IT**ting Multipl**E** Sclerosis". All participants provided written informed consent after full explanation of the protocol.

The study was conducted in accordance with the International Conference on Harmonisation (ICH)/WHO Good Clinical Practice Standards.

The full protocol is also available by the link: http://www.chu-caen.fr/gesdoc/docrecherche/ProtocoleSEPamendement14_05122009.pdf.

2.2. Participants

The participants included males and females, 18–60 years of age, with a diagnosis of RR-MS [19] and presenting with a cognitive complaint and/or demonstrating moderate cognitive impairment. The patients were required to have an EDSS score [20] ≤5.5, a Dementia Rating score [21] ≥130, a PASAT score [22] >15 but lower than the mean −1.5 SD of the control value, according to age, gender, and education level, of a healthy French reference cohort [23].

Prior to randomization, the patients were treated for at least three months with one of the following immunomodulator or immunosuppressive treatments:

- Interferon β
- Glatiramer acetate
- Azathioprine
- Methotrexate
- Mycophenolate mofetil
- Natalizumab.

Patients who benefited from mitoxantrone or cyclophosphamide were eligible only if the treatment had ended more than six months prior to randomization.

Women were required to use a medically acceptable method of contraception.

The exclusion criteria consisted of a progressive form of MS or a tumoral form of MS visible on MRI examination, MS relapse in the previous 30 days, intravenous or oral corticoid treatment in the month preceding randomization, any symptomatic or non-medical cognitive therapy or neuropsychological training for cognitive disorders, antidepressant or anxiolytic treatment in the 3 months prior to randomization, a score > 19 on the Montgomery Asberg Depression Rating Scale (MADRS) [24],which was suggestive of significant depressive symptoms, other diagnosed psychiatric conditions, or a known allergy to memantine.

2.3. Study design

The present study was a multicenter (19 centers), 52-week, double-blind, placebo-controlled, parallel group, randomized trial. Eligible patients were assigned to receive a placebo or memantine (twice daily), and the maintenance dose of 20 mg per day was achieved through an upward adjustment of 5 mg per week over the first 3 weeks. Down titration was not permitted during the present study. Memantine (Ebixa®) and the placebo were provided by Lundbeck (Copenhague-Valby Denmark). The data were collected in the Department of Neurology at