Original Investigation

Effect of homotaurine in patients with cognitive impairment: results from an Italian observational retrospective study


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Background & Aims: This observational retrospective study aimed at evaluating the effects of one-year administration of homotaurine (tramiprosate) in a sample of patients presenting with symptoms of mild cognitive impairment.

Methods: Patient’s demographic data and medical history are reported. Each patient performed brain imaging and neuropsychological assessment to reach the diagnosis. Each patient assumed 100 mg total dose of homotaurine/day. The evolution of the cognitive decline over time was evaluated by means of the Mini Mental State Examination (MMSE).

Results: 245 patients from 28 different centres in Italy were recruited. Significant improvements from baseline expressed as mean MMSE total score were observed in patients with aMCI at months 8 and 12 (p < 0.0001), and in those with mMCI at month 4 (p < 0.05).

Conclusions: Administration of homotaurine revealed beneficial effects in our sample population of MCI patients. Our results indicate clearly that homotaurine may well be considered as a potential symptomatic treatment for cognitive symptoms. Further research is however needed to clarify whether this compound could influence the progression of cognitive decline.

Key words: Homotaurine, Mild cognitive impairment, Alzheimer's disease
INTRODUCTION

Cognitive decline consists in an acquired progressive decrease of efficiency of cognitive function (e.g. attention, executive function, learning and memory, language, perceptual-motor, and social cognition) that is more marked than the physiological age-related decline 1,2. The spectrum of severity of neurocognitive disorders varies from mild cognitive impairment (MCI) to the most severe cases of dementia. In this view, MCI should be considered as a transitional state evolving from normal cognition to cognitive impairment with essentially preserved functional abilities 3,4. MCI as a clinical category is difficult to put in the correct frame. MCI is a clinical entity often diagnosed in our hospital practice, and the need for a pharmacological treatment to alleviate cognitive symptoms is of course welcome. In this view, recent clinical and population-based data suggest that MCI have a prevalence of 10-20% for adults aged ≥ 65 years, a condition that resulted strictly associated with population aging 5. Despite the extensive research in the past few years, the current treatment options for MCI have a limited impact on the pathophysiology of the disease and treatments acting on disease progression remain an unmet medical need. Recent research on AD pathogenesis has highlighted the role of amyloid beta (Aβ) cascade events 10. Despite multifaceted, Aβ-based theory claims that Aβ aggregates and forms oligomers, peptides with highly toxic effects on synapses. Oligomers produced in condition of sustained synaptic transmission, induce stable change in synaptic plasticity mechanisms leading to impairment of neural transmission, oxidative stress and chronic inflammatory response, responsible for neuronal degeneration 11. These findings led to the development of potential anti-amyloid therapies and, overall, of new pharmacological interventions since the very early stages of AD-related pathology 12. Among them, homotaurine (tramiprosate), a natural aminosulfonate compound that is present in different species of marine red algae, has shown anti-amyloid effects with neuroprotective properties in a number of in-vitro and in-vivo models 13. The therapeutic efficacy of homotaurine has been investigated in clinical trials as well. In the ALPHASE study, conducted in more than 1000 patients with mild to moderate AD, treatment with homotaurine for 18 months was associated with a trend towards benefit on memory, language and praxis skills 14, and reduced hippocampus volume loss 15. The positive effects of homotaurine supplementation on hippocampus atrophy and memory were recently confirmed in patients with aMCI 16. Furthermore, the potential beneficial effects of homotaurine in other diseases than cognitive impairment were investigated. Dose-dependent neuroprotection against ischemic stroke was demonstrated in in vitro and in vivo models 17. In patients with Parkinson's disease (PD) and cognitive impairment, homotaurine was shown to have beneficial effects on sleepiness and possibly on memory 18.

Based on this background, we have considered of interest to collect retrospective data of patients treated with homotaurine according to common clinical practice in Italy, in order to add further information on the effects on cognitive function in patients with cognitive impairment seeking for specialist consultation.

PATIENTS AND METHODS

This observational, retrospective, non-interventional study was conducted in 28 sites in Italy. The main objective of the study was to collect clinical information on patients diagnosed as mildly cognitive impaired according to Petersen criteria 3. All patients underwent a complete clinical investigation, including medical history, neurological examination, mini mental state examination (MMSE), a complete blood screening (including routine exams, thyroid hormones, level of B12), neuropsychological examination, neuropsychiatric evaluation, and neuroimaging consisting of magnetic resonance imaging (1.5 T MRI).

The objective of this study was to evaluate the effect of homotaurine administration (100 mg/day) in the sample patients with a diagnosis of MCI as a whole. Then, we evaluated the effect of homotaurine in different subcategories of MCI: aMCI, mMCI, vascular dementia (VAD) and MCI due to other causes (in this case brain traumas, Parkinson's disease, post-hemorragic heamatoma). Treatment with homotaurine was at the discretion of the physician, according to the local standard of medical care, and the decision of starting treatment with homotaurine was independent from the inclusion in the study. Patients with aMCI and mMCI did not assume
any cognitive enhancer drug (i.e. antidepressants, mood stabilizers etc.) at the beginning of the study. Patients with AD and VAD assumed stable therapy with donepezil 10 mg or rivastigmine patch 9.5 mg since 6 months before study start. Patients with PD assumed pharmacological treatment with L-Dopa or dopamine agonists, and their doses remained unchanged since at least 3 months before the study start. Post-haemorrhagic hematoma patients assumed pharmacological treatment for hypertension.

The evolution and outcome of the cognitive symptoms over time were evaluated my means of the Mini Mental State Examination (MMSE), which was performed at the baseline, 4, 8 and 12 months.

Data are reported as mean value and standard deviation (SD). The evolution over time of MMSE total score was analysed by means of an analysis of variance (ANOVA) and the categorical results from baseline to month 12 (improved, unchanged, worsened) were analysed by means of a pseudo-marginal Markov chain method. The Markov Chain Monte Carlo (MCMC) method was used for imputation of missing data of MMSE. The analysis of the results of MMSE was performed in each subgroup of diagnosis. The study was performed according to the Declaration of Helsinki.

RESULTS

245 patients were enrolled in this study. Of them 106 presented with aMCI, while 47 with mMCI. 32 presented with incipient AD, 12 had a diagnosis of VAD, based on the presence of strategic infarcts (mainly anterior thalamic, frontal or fronto-parietal) or diffused vascular burden of the brain microvasculature. 48 patients had a diagnosis of MCI with a history of other neurological pathology such as PD, brain subdural hematomas or traumas. Homotaurine was well tolerated and side effect were never reported by patients and their care givers.

The mean (± SD) age in the total population was 72.9 ± 9.7 years (median 75 years, range 30-94 years), and was similar in males (73.3 ± 9.3 years) and in females (72.6 ± 9.8 years). The mean age was higher in patients with AD (77.1 ± 6.8 years) and in those with VAD (77.9 ± 8.0 years) than in the other subgroups. The distribution of age range showed that the highest prevalence was in the range of 76-80 years (86 patients, 27.5%), followed by the ranges 71-75 years (53 patients, 16.9%) and 81-85 years (55 patients, 15.6%). Consistently with data of mean age, AD and VAD were prevalent in older age ranges, whereas mMCI and aMCI were more frequent in younger patients. Data of mean age at onset of the disease reflected those of age at the time of study entry (Tab. I). At baseline, patients with aMCI or mMCI had a higher mean MMSE total score (i.e. a lower cognitive impairment) than those with AD or vascular dementia. In particular, MMSE score of the aMCI group of patients was 25.1 ± 3.0, MMSE score of mMCI was 25.0 ± 2.7, AD patients scored 20.3 ± 4.2, VAD patients scores 21.7 ± 4.7, while patients with MCI due to other diagnosis scored 24.9 ± 3.7 Improvement vs. baseline in mean MMSE total score was observed in patients with diagnosis of aMCI and mMCI. Conversely, a general cognitive decline was observed in patients with AD and VAD. The increase vs baseline in mean MMSE score was statistically significant in patients with aMCI at months 8 and 12 (month 8: 27.2 ± 2.6, month 12: 26.9 ± 3.2; p < 0.0001 for both comparison), in those with mMCI at month 4 (27.3 ± 2.6; p < 0.05), and in those with MCI due to other diagnoses at month 12 (26.1 ± 3.8; p < 0.01). The decrease in mean MMSE score was statistically significant at month 12 vs baseline in patients with AD (18.0 ± 3.6; p < 0.0001). Figure 1 shows the results of the MMSE at baseline and at the post-baseline time points.

DISCUSSION

The aim of this retrospective observational study was to evaluate the cognitive effects of homotaurine administration (100 mg/day) in a population of individuals with diagnosis of MCI, treated for 12 months. Cognitive effects were evaluated in terms of mean MMSE total score. Main findings of our study showed that patients with diagnosis of aMCI, and to a lesser extent those with mMCI, showed marked improvement from the
treatment with homotaurine. MMSE improvement was sustained up to 12 months of observation, whereas the maximum improvement in mMCI patients was observed after 4 months from the start of treatment. Patients with diagnosis of AD or vascular dementia did not apparently benefit from the treatment. Furthermore, patients with MCI due to non-AD related pathology showed improvement as well. The latter subcategory, although heterogeneous, indicates that in MCI due to brain traumas and/or hemorrhagic hematomas, and to Parkinson’s disease, homotaurine induces a measurable and long-lasting efficacy in terms of cognitive functions. Hence, we can conclude that homotaurine administration is effective on cognitive symptoms of MCI individuals, both in AD and non-AD pathologies. Reasons of such results however need to be interpreted with caution, and recent experimental and clinical data yielded on homotaurine effects on cognitive function could be helpful. Homotaurine is known to act through a double mechanism: the modulatory activity on cortical GABA A receptors, and the anti-amyloid activity, both effects well documented in vitro studies. Recently two main studies has been published on the effects of homotaurine administration in MCI subjects due to AD pathology. First, an electrophysiological study showed the ability of homotaurine to modulate short latency afferent inhibition (SLAI) after 4 weeks of treatment. SLAI is considered an in vivo measure of central cholinergic transmission thus suggesting for homotaurine a modulatory effect on cortical GABA interneurons activity and in the regulation of the cholinergic control of cortical excitatory transmission. In this view, it is known that cortical GABA transmission is involved in several functions ranging from the control of the excitatory activity to the regulation of parietal-frontal connections. These structures are strictly involved in the control of executive functions, memory and attention, co-operating with cholinergic transmission. Thus, it is conceivable to suppose that some of the effects of homotaurine observed in our MCI subcategories might be related to its effect on cortical GABA A receptors. The second recent study performed in patients with aMCI showed that patients treated with homotaurine for one year had decreased volume loss in the bilateral hippocampus tail and in other brain areas, such as the bilateral fusiform gyrus and the right inferior temporal cortex. These morphological changes in patients treated with homotaurine were paralleled by beneficial effects in the short component of episodic memory, compared to untreated subjects. Both studies clearly confirmed a valuable effect of homotaurine on MCI individuals. However, whether the effects observed on cognition are attributable to GABA modulatory activity, anti-amyloid effects or both remains to be established. Moreover, the finding that homotaurine concur to reduce brain atrophy, although indirectly, led to suppose that an effect on amyloid metabolism is likely. As claimed by amyloid hypothesis cascade, Aβ pathology occur years before the appearance of cognitive decline, and initiate a pathological process that tau pathology make manifest. This hypothesis would also highlight the importance of an early correct diagnosis of MCI and AD. Within this context, the identification of pathogenic Aβ by means of molecular neuroimaging or biological markers will help identify cases at the earliest stages

Table I. Demographic data and disease characteristics overall and by type of diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>aMCI (N = 106)</th>
<th>mMCI (N = 47)</th>
<th>AD (N = 32)</th>
<th>VD (N = 12)</th>
<th>Other (N = 48)</th>
<th>Total (N = 245)</th>
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<tr>
<td>Age (years), mean ± SD</td>
<td>71.2 ± 10.6</td>
<td>73.5 ± 7.1</td>
<td>77.1 ± 6.8</td>
<td>77.9 ± 8.0</td>
<td>72.6 ± 9.9</td>
<td>72.9 ± 9.7</td>
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<td>Age range, N (%)</td>
<td></td>
<td></td>
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<td>66-70 years</td>
<td>21 (13.9%)</td>
<td>11 (21.2%)</td>
<td>2 (5.3%)</td>
<td>1 (6.7%)</td>
<td>9 (15.8%)</td>
<td>44 (14.1%)</td>
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<tr>
<td>71-75 years</td>
<td>22 (14.6%)</td>
<td>13 (25.0%)</td>
<td>4 (10.5%)</td>
<td>3 (20.0%)</td>
<td>19 (33.3%)</td>
<td>53 (16.9%)</td>
</tr>
<tr>
<td>76-80 years</td>
<td>37 (24.5%)</td>
<td>15 (28.8%)</td>
<td>12 (31.6%)</td>
<td>3 (20.0%)</td>
<td>86 (27.5%)</td>
<td>182 (58.1%)</td>
</tr>
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<td>≥ 86 years</td>
<td>7 (4.6%)</td>
<td>8 (15.4%)</td>
<td>14 (36.8%)</td>
<td>7 (46.7%)</td>
<td>55 (15.6%)</td>
<td>8 (2.6%)</td>
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<td>Sex, N (%)</td>
<td></td>
<td></td>
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<tr>
<td>Males</td>
<td>61 (40.4%)</td>
<td>30 (60.0%)</td>
<td>23 (60.5%)</td>
<td>13 (86.7%)</td>
<td>122 (50.8%)</td>
<td>182 (51.8%)</td>
</tr>
<tr>
<td>Females</td>
<td>22 (42.3%)</td>
<td>13 (24.5%)</td>
<td>2 (3.5%)</td>
<td>25 (43.9%)</td>
<td>123 (39.3%)</td>
<td>30 (12.3%)</td>
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<td>-</td>
<td>5 (1.6%)</td>
<td>8 (2.6%)</td>
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<tr>
<td>Age at onset of symptoms (years), mean ± SD</td>
<td>69.4 ± 10.6</td>
<td>70.9 ± 7.8</td>
<td>73.5 ± 8.0</td>
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<td>64 (42.4%)</td>
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<td>7 (18.4%)</td>
<td>7 (46.7%)</td>
<td>18 (31.6%)</td>
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<td>46 (88.5%)</td>
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<td>1 (1.9%)</td>
<td>-</td>
<td>-</td>
<td>2 (3.5%)</td>
<td>5 (1.6%)</td>
</tr>
</tbody>
</table>

Abbreviations: N: number of patients; MCI: mild cognitive impairment; aMCI: amnestic mild cognitive impairment; AD: Alzheimer’s disease; VD: vascular dementia; SD: standard deviation
of the disease process \cite{26,27}. The early diagnosis of MCI relies on the hypothesis that pharmacological interventions with disease-modifying compounds are more likely to produce clinically relevant benefits if started early before the progression towards dementia \cite{28}. With this respect, the apparent lack of effects in patients with AD enrolled in this study may be due to the small sample with this diagnosis, which could also have included patients with advanced age that were less likely to benefit from treatment with homotaurine than younger subjects. Post-hoc analyses of results of the ALPHASE study and of other studies have shown that beneficial effects of homotaurine were mainly observed using adjusted predictive models or in selected groups of patients. An exploratory analysis performed in the subgroup of 312 participants in the ALPHASE study who underwent longitudinal volumetric resonance imaging (VMRI) and were evaluable for assessing hippocampus volume changes \cite{29}, showed that homotaurine slowed hippocampal atrophy and revealed some evidence of a beneficial effect on cognition. A post-hoc analysis of the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) observed in the ALPHASE study revealed statistically significant differences, in favour of homotaurine vs placebo, thus suggesting that homotaurine may have beneficial and protective effects on memory, language and praxis in mild to moderate AD patients \cite{13}.

Further analyses in 599 patients of the ALPHASE study with at least one ε4 allele of apolipoprotein E gene (APOE4+), i.e. the major genetic risk factor for AD \cite{30}, showed that homotaurine given for 18 months in addition to acetylcholinesterase inhibitors and/or memantine produced a clinically meaningful improvement in cognition and function \cite{13}.

The same findings were observed in an analysis that included 909 APOE4+ patients from the two phase III trials on homotaurine, i.e. the ALPHASE study conducted in North America and another study conducted in Europe. Furthermore, a higher efficacy of homotaurine was observed in the APOE4/4 homozygous subgroup compared to the heterozygotes patients, thus suggesting a gene dose effect of APOE4, potentially due to larger amyloid burden in APOE4/4 homozygotes. These novel findings indicate that further research is needed to identify biomarkers that help in selecting the subgroups of patients which may have the highest benefit from treatment with homotaurine \cite{31}.

Of course our study is unable to indicate a clear mechanism of action, although confirm the positive effects on cognition. Despite these limitations, available data have shown that patients with a diagnosis of MCI, whatever the cause, had improvements or stabilization of cognitive decline, whereas the results in patients diagnosed with AD or vascular dementia, although evaluated in small samples, did not show evidence of benefit following treatment with homotaurine. Currently, no drug has been proven effective in the treatment of MCI \cite{32} and appropriate strategies to treat MCI and prevent the progressive decline of cognitive functions include the control of vascular risk factors, treatment of lifestyle-related diseases and training on cognitive function \cite{33}.

In conclusion, this study provides further information on the effectiveness of homotaurine in the management of patients with cognitive impairment. The results have shown that patients with MCI were more likely to benefit from treatment with homotaurine. Prospective controlled studies conducted in adequate samples are needed to assess the long-term effectiveness of homotaurine, given as monotherapy or in addition with other drugs, in the management of patients with different stages of cognitive decline.

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**Declaration of Sources of Funding**

None.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


17 Wu S, Yue Y, Tian H, et al. Tramiprosate protects neurons against ischemic stroke by disrupting the interaction between PSD95 and nNOS. Neuropharmacology 2014;83:107-17.


