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A 6-month, open-label study of memantine in patients with frontotemporal dementia

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SUMMARY

Objective To evaluate safety and effects on cognition and behavior of memantine 20 mg/day in the treatment of patients with frontotemporal dementia (FTD).

Methods This was a single-center, 6-month, open, uncontrolled study. Sixteen outpatients with a diagnosis of FTD were enrolled.

Results On the CIBIC plus 26 weeks after baseline four of the 16 patients were minimally improved, four were unchanged, seven were minimally worse and one patient was moderately worse. Neither the Neuropsychiatric Inventory nor the Frontal Behavioral Inventory demonstrated statistically significant differences in behavior between baseline and final visit. There was an increase in the total Alzheimer's Disease Assessment Scale score, reflecting a decline in cognitive performance. Executive functions as well as activities of daily living and extrapyramidal motor symptoms (EPMS) remained unchanged during the trial.

Conclusion The number of patients was small, so that the evidence given by statistical tests is limited. Thus, the present study can only show trends regarding drug effects. As memantine is well-tolerated, further randomized and controlled studies should be conducted to evaluate drug efficacy. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — frontotemporal dementia; semantic dementia; memantine; drug-trial; treatment

INTRODUCTION

Historically, FTD has been considered a rare cause of dementia, but presently it is believed to account for 3–20% of all dementias (Neary, 1999; Barker *et al*., 2002; Rosso, 2003). FTD is a clinically, anatomically and histopathologically heterogeneous disorder. Frontally predominant (frontal variant of FTD, fvFTD) and temporally predominant (temporal variant of FTD, tvFTD, also known as semantic dementia) subtypes have been described.

Changes in personality and social conduct are the outstanding symptoms of fvFTD, however, deterioration of cognitive abilities must not be overlooked. Impairments of executive functions, memory and language invariably occur. Neurological signs include incontinence and extrapyramidal motor symptoms (EPMS) (Diehl-Schmid *et al*., 2007). FvFTD is a progressive and malignant disorder, with a median survival time from symptom onset of 6 (Hodges *et al.*, 2003) to 14 (Diehl-Schmid *et al*., 2006) years.

TvFTD is associated with neurodegeneration predominantly in the anterior temporal lobes. The most prominent clinical picture of tvFTD is a progressive semantic impairment. Patients are significantly impaired in word comprehension and confrontation naming (Diehl *et al*., 2005). Although semantic deficits dominate the clinical picture, behavioral alterations also occur (Liu *et al*., 2004; Seeley *et al*., 2005).

It has been shown that patients with FTD show deficiencies in the serotonin neurotransmitter system (for a review see Huey *et al*., 2006). In addition, there is evidence of a dopaminergic deficit in FTD from various CSF- and neuroimaging-studies (Sjögren

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et al., 1998; Sperfeld *et al*., 1999; Rinne *et al*., 2002). Furthermore, it has been found that AMPA and NMDA-receptors are reduced in the frontal and temporal cortices in patients with FTD (Procter *et al*., 1999). A loss of glutamatergic pyramidal cells and immunoreactive GABAergic neurons in the frontal and temporal cortices has also been found (Ferrer, 1999).

Memantine is a moderate-affinity non-competitive antagonist of the NMDA receptor. It facilitates physiological glutamate-mediated neurotransmission, protects neurons against glutamatergic excitotoxicity, and may have neuroprotective effects by reducing toxic calcium influx. Moreover, memantine modulates dopaminergic systems indirectly by enhancing dopamine release. In patients with moderate to severe AD memantine provides statistically significant treatment effects relative to placebo in the areas of cognition, activities of daily living, and global change (Winblad and Poritis, 1999).

Based on this evidence we hypothesized that memantine has the potential of enhancing glutamate- and dopamine- mediated neurotransmission in FTD, and that this would translate to improvement of cognitive abilities and of non-cognitive symptoms.

OBJECTIVES OF THE STUDY

(1) To determine the safety of 20 mg/day memantine in patients with FTD.
(2) To evaluate the effects of memantine treatment on five clinically relevant domains including global assessment, behavioral disturbances, general intellectual ability, executive functions/attention and EPMS.

PATIENTS AND METHODS

We conducted a single-center, open, uncontrolled study with a treatment duration of 6 months (including a 3-week titration phase), which was rater-blind (the rater did neither know the patient's diagnosis nor in which study the patient participated). Sixteen outpatients were enrolled who had been diagnosed with FTD according to the Lund-Manchester criteria (The Lund and Manchester Groups, 1994) and had a reliable caregiver who was able to accompany the patient to all study visits and to supervise medication intake during the course of the study. Diagnostic procedures consisted of history, psychiatric and neurological examination as well as laboratory screening. Patients underwent neuropsychological testing including the Mini-Mental-State-Examination (MMSE) (Folstein *et al*., 1975), and the German version of the Consortium to Establish a Registry of Alzheimer's Disease Neuropsychological Assessment Battery (CERAD-NAB) (Monsch, 1997). All patients underwent cranial computed tomography or magnetic resonance imaging to exclude focal lesions, and cranial 18F-FDG-PET to determine brain metabolic activity. Patient classification into fvFTD and tvFTD was based on clinical symptoms, neuropsychological test results and findings on 18F-FDG-PET by consensus of two experienced gerontopsychiatrists (J-DS, AK). Patients with fvFTD showed a predominantly frontal hypometabolism; anterior temporal areas were affected to a lesser extent in most patients. All subjects with tvFTD showed a hypometabolism exclusively in the temporal lobes. Only patients with an MMSE score of at least 15 points and a Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994) score of at least 6 points were included. Patients were excluded from the study if any new psychotropic medication had been initiated within 8 weeks prior to baseline, and if they had been treated with cholinesterase inhibitors or other antidementia drugs including memantine or antidepressants within 26 weeks before baseline.

The study was approved by the local Ethics Committee, Faculty of Medicine, Technische Universität München. Written informed consent was obtained from all study participants.

Primary and secondary endpoints of the study are listed in Table 1.

Safety was assessed by monitoring adverse events, serious adverse advents, vital signs, and routine laboratory values.

After screening four visits were scheduled: baseline (= visit 1) at week 0, visit 2 at week 4, visit 3 at week 12, and the final visit 4 at week 26.

Statistical analysis

Data were analysed using the SPSS 11.0 software package (SPSS for the Macintosh, SPSS Inc., Chicago, IL, 2003). Differences in the results in the NPI, FBI, FAB, CWT, TMT-A, TMT-B and the UPDRS-III between baseline and the final visit after 26 weeks were analysed using the Wilcoxon signed-rank test for related samples.

Results were considered as statistically significant at a p-value < 0.05. The analyses were performed on all patients included in the study (intent-to-treat population, ITT, $n = 16$) using the last observation carried forward (LOCF) method. As a sensitivity analysis the calculations were repeated for the

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Table 1. Endpoints of the study

Primary endpoints	Clinician's Interview-Based Impression of Change with Caregiver Input (CIBIC-plus) (Guy, 1976) Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994) Frontal Behavioral Inventory (FBI) (Kertesz *et al*., 1997)
Secondary endpoints	Alzheimer's Disease Assessment Scale (ADAS-cog) (Rosen *et al*., 1984) Frontal Assessment Battery (FAB) (Dubois *et al*., 2000) Trail Making Test A (TMT-A) and B (TMT-B) (Reitan, 1958) Color Word Test (CWT) (Fleischmann and Oswald, 1994) BAYER Activities of Daily Living Scale (B-ADL) (Hindmarch *et al*., 1998) Unified Parkinson's Disease Rating Scale subsection III (motor) (UPDRS-III) (Fahn *et al*., 1987)

subgroups of patients with fvFTD ($n = 9$) and tvFTD ($n = 7$).

RESULTS

Demographic information

Sixteen patients were included in the study. Demographic data and mean scores on the MMSE are provided in Table 2.

Compliance with the study protocol

Three of the 16 patients (19%) dropped out of the study before the scheduled final visit at week 26. The reasons for premature termination were: (1) new onset of depression (5 days after baseline); (2) agitation/psychosis (after visit 3); and (3) poor compliance (after visit 3).

Safety of memantine

We did not observe clinically relevant changes regarding routine laboratory parameters or vital signs. Following adverse events were reported: acne, cold, fall, pain of shoulder, dizziness, recurrent bronchitis, tinnitus, fracture of the humerus, fracture of the radius, recurrent gout, contusion of the wrist, craniocerebral injury, edema of the legs, absolute arrhythmia, depression, psychosis (serious adverse event). Apart from depression, which was possibly related to study medication, none of the adverse events was judged as related to study medication.

Efficacy

Primary endpoints. The results of the CIBIC-plus at the final visit 26 weeks after baseline are provided in Table 3.

The mean CIBIC-plus score at the final visit was 4.3 (SD = 0.95).

There were no statistically significant differences on the NPI and FBI between baseline and final visit (total scores: NPI baseline: 19.4 ± 7.3; NPI final visit: 20.7 ± 13.4; FBI baseline: 26.1 ± 9.7; FBI final visit: 26.9 ± 16.8). Furthermore, there were no significant changes of the subitems of the NPI

Table 2. Demographic data and mean score on the MMSE of the whole patient group (fvFTD + tvFTD) and the subgroups (mean ± SD; (min–max))

	N	Female/male	Age (years)	Education (years)	Age onset (years)	Duration of disease (years)	MMSE (total score)
fvFTD + tvFTD	16	6/10	67.6 ± 5.3 (60–78)	12.4 ± 3.6 (8–19)	63.2 ± 6.0 (54–73)	4.5 ± 1.9 (2–8)	25.1 ± 3.4 (15–27)
fvFTD	9	4/5	69.0 ± 5.6 (60–78)	11.2 ± 3.3 (8–18)	64.8 ± 6.5 (55–73)	4.1 ± 1.7 (2–8)	25.2 ± 4.3 (15–29)
tvFTD	7	2/5	65.7 ± 4.4 (61–74)	13.9 ± 3.7 (10–19)	61.1 ± 5.0 (54–69)	5.0 ± 2.2 (2–8)	24.8 ± 1.8 (22–27)

Table 3. Primary endpoint, CIBIC plus

N	1 Markedly improved	2 Moderately improved	3 Minimally improved	4 No change	5 Minimally worse	6 Moderately worse	7 Markedly worse
16	—	—	4	4	7	1	—

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Table 4. Secondary endpoints: mean scores at baseline and final visit (mean, SD in parentheses)

	Baseline	Final visit	*P*-value for change
ADAS-cog	49.5 (12.3)	59.4 (17.4)	**0.02**
FAB	12.4 (3.3)	12.4 (4.8)	0.15
CWT [seconds]	55.0 (52.2)	53.9 (40.6)	0.68
TMT-A [seconds]	79.9 (47.3)	74.6 (34.3)	0.51
UPDRS	5.2 (5.3)	4.9 (3.0)	0.58
B-ADL	4.4 (2.1)	4.9 (2.7)	0.09

Bold value is statistically significant.

(delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleeping disturbances, eating disturbances) between baseline and the final visit.

Secondary endpoints. We did not include the TMT-B in the analysis, as the majority of patients was not able to complete the test within the given time limit. In the whole group of patients we found a significant increase in the total score on the ADAS-cog ($p = 0.02$) between baseline and the final visit, which indicates cognitive deterioration (Table 4).

Subgroup analyses

To determine whether the results were influenced by the clinical subtype of FTD, in a second step the analyses were calculated for patients with fvFTD ($n = 9$) and tvFTD ($n = 7$) separately.

The results of the CIBIC-plus at the final visit 4 were as follows: 33.3% of the patients with fvFTD and 14.3% of the patients with tvFTD minimally improved. There was no change in 11.1% of the fvFTD group as compared to 42.9% in the tvFTD group. Worsening was observed in 55.5% of the patients with fvFTD and in 42.9% of the patients with tvFTD.

In the fvFTD group we found a significant increase in the time required to accomplish the TMT-A ($p = 0.05$). Furthermore, there was a significant increase in the B-ADL, reflecting a worsening of activities of daily living ($p = 0.02$).

The subgroup of patients with tvFTD improved significantly ($p = 0.04$) in the FBI between baseline and the final visit.

DISCUSSION

To date, very few treatment options are available for patients with FTD that are supported by the results of clinical trials. Pharmacological interventions used for FTD are based on neurotransmitter replacement strategies. Anecdotal reports and a number of small, and uncontrolled studies have shown that treatment with antidepressants (Chow and Mendez, 2002) or atypical antipsychotics (Moretti *et al*., 2003b) can be associated with improvement of behavioral symptoms. Moretti *et al*. (2004) showed a decrease of behavioral disturbance by rivastigmine, demonstrated by a significant reduction of the NPI total score between baseline and final visit after 12 months. However, rivastigmine treatment did not prevent the deterioration of cognitive ability.

A small number of randomized studies found positive effects of serotonergic agents in patients with FTD. Pasquier *et al*. (2004a) reported a significant decrease in the NPI and a modest improvement of clinical severity after a 6-week treatment with trazodone. In another study Moretti *et al*. (2003a) found that patients treated with paroxetine showed significant improvements in behavioral symptoms as assessed with the NPI compared to patients treated with piracetam after a 14-month treatment period. Baseline scores of global performance, cognition and planning capacities remained stable whereas the performance of attention and abstract reasoning decreased.

Following the approval of memantine for the use in moderate to severe Alzheimer's disease (AD) by the FDA in the USA and by the EMEA in Europe there has been increasing interest in its efficacy in FTD. A few trials are under way, but to date no published data from controlled clinical trials with memantine in FTD are available. There is one preliminary report on 10 of 15 FTD subjects who completed a 6-month open-label study of memantine (Scharre *et al*., 2005): the drug was well tolerated, but no changes were observed on cognition (ADAScog), behavior (total NPI), activities of daily living, or clinical dementia rating scores. Regarding NPI domains separately, there was some improvement of disinhibition. A case series of three patients with FTD, who were treated with memantine, was published recently (Swanberg, 2007). All three patients showed an improvement in the total NPI score with specific improvements in the subscale scores of apathy, agitation and anxiety.

The present study demonstrates that memantine is well tolerated and safe in the treatment of patients with FTD.

Changes of the clinical status of the patients were assessed using the CIBIC plus. Overall, 50% of the patients were either stabilized or minimally improved. The mean CIBIC-plus score at the final visit was 4.3,

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indicating minimal worsening. Similar outcomes on the CIBIC plus were found in a 24-week randomized controlled trial comparing efficacy and safety of memantine in mild to moderate AD. Patients receiving memantine had a mean CIBIC plus score of 4.3 after 24 weeks, and declined significantly less than the placebo group (Peskind *et al*., 2006).

Behavioral disturbances, as measured with the NPI and FBI, did not change significantly between baseline and last visit in the whole group of patients. However, there was a significant improvement on the FBI in patients with tvFTD. With regard to the small sample size this is a potentially important finding. It should be noted, however, that there were no parallel changes on the NPI. The FBI has been specifically designed for patients with dementia caused by FTD and probably has greater sensitivity in the assessment of behavioral symptoms typical for FTD.

In the whole group of patients we found a significant increase in the total ADAS-cog score, a mean difference of 9.9 points between baseline and the final visit indicating quite a rapid decline of cognitive performance. This result is difficult to interpret. Previous studies have shown that the average annual decline on the MMSE is at least 5 points, which is more rapid than commonly reported in AD (Pasquier *et al*., 2004b). But so far, there are no studies about the longitudinal changes of patients' performance in extensive neuropsychological tests. Thus, we do not know, if the observed decline corresponds with the decline that would have been observed in untreated patients. Furthermore, it is difficult to explain, why patients worsened in the ADAS-cog, whereas results of tests of executive functions remained stable in the present study.

The current data need to be interpreted with caution. The number of patients was small, particularly with regard to the comparison between the two subgroups fvFTD and tvFTD, so that the evidence given by statistical tests is limited. Multi-center studies need to be organized to obtain larger patient samples. Furthermore, the study design was open-label and did not include a control group. Not much is known about the clinical progression of FTD. There is some evidence that symptom progression shows a large individual variability, but no studies have been conducted to date to investigate the natural course of FTD and the mean annual decline in various tests in a large untreated sample. On these grounds it remains uncertain whether stability in a number of tests can be attributed to an effect of the study medication.

All in all, the present exploratory study can only show trends regarding drug effects. As memantine is well-tolerated, further randomized and controlled studies should be conducted to evaluate drug efficacy.

CONFLICT OF INTEREST

Hans Förstl receives honoraria as consultant for Lundbeck A/S, Copenhagen/Denmark and Merz, Frankfurt/Germany. Potential conflicts of interest can be excluded.

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