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Original articles

Donepezil in the treatment of mild to moderate Alzheimer's disease : report of a Belgian multicenter study

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Abstract

In this report the results of a Belgian multicenter 24-week open-label study with donepezil in the treatment of mild to moderate Alzheimer's disease are described. Efficacy and safety were evaluated in a sample of 200 patients recruited in 25 Belgian centers. No significant changes could be found in cognition and behaviour over this 6-month period. Changes in daily functioning were small. Safety data were comparable to those reported in international trials. These results suggest that the findings of more robust double-blind, placebo-controlled studies can be confirmed in real life situations.

Introduction

Numerous studies have investigated the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease (AD). Beneficial effects of these agents on cognition, activities of daily living and behaviour have convincingly been demonstrated, as well as significant reductions on caregiver stress (Rogers S. L. *et al.*, 1998 ; Rösler M. *et al.*, 1998 ; Corey-Bloom J. *et al.*, 1998 ; Rösler M. *et al.*, 1999 ; Tariot P. N. *et al.*, 2000 ; Raskind M. A. *et al.*, 2000 ; Farlow M. R. *et al.*, 2000 ; Winblad B. *et al.*, 2001 ; Doody R. S. *et al.*, 2001). Subsequently, the use of this class of drugs has been recommended in recent guidelines concerning the treatment of AD (Doody R. S. *et al.*, 2001).

Donepezil is a reversible and selective inhibitor of acetylcholinesterase. The effects of donepezil in the treatment of mild to moderate AD have been reported in a number of multinational and multicenter studies (Rogers S. L. *et al.*, 1998 ; Winblad B. *et al.*, 2001 ; Doody R. S. *et al.*, 2001). The present study aims to report on the effectiveness and safety of donepezil in a Belgian multicenter study.

Patients and methods

The present study was a 24-week open-label, multicenter study of ambulatory patients with clinically diagnosed mild to moderate probable or possible AD. Twenty-five centers participated in this study. A total of 200 patients were enrolled into the study (DON-B-97-001). Exclusion criteria are listed in table 1. There were 132 women (66%) and 68 men (34%). Mean age at the start of the study was 72.2 yrs (SD 7.4 yrs). Seventy-four (37%) of these patients previously participated in a 3-month open-label multinational experience trial (DON-NY-96-003-322), while 126 (63%) did not (designated group I and II, respectively). The inclusion and exclusion criteria for this multinational study were identical to the ones used here. Over the 3-month treatment period of this multinational study beneficial effects of donepezil had been demonstrated on cognition and social interaction, using Mini-Mental State Examination (MMSE) scores (Folstein M. *et al.*, 1975) and caregiver diaries as primary outcome measures.

Written informed consent was obtained from the patients and their caregiver or legal guardian before the screening visit took place. Local Ethics Committees approved of the protocol in all of the participating centers. Following a baseline visit, 4 study visits took place in the 24-week study period (weeks 4,8,16 and 24). During the first 8 weeks patients received 5 mg of donepezil. After that, if clinically indicated, the dosage could be increased to 10 mg. Patients who entered the present study following the multinational experience trial could be maintained on 10 mg if this was the daily dosage at the end of this multinational study. Furthermore patients on 5 mg after this previous trial could be switched to 10 mg at any visit if clinically indicated.

Cognitive outcome was evaluated using the MMSE (Folstein M. *et al.*, 1975). Activities of daily living were evaluated using the Activities of Daily Living/Physical Self-maintenance scale (ADL) (Katz S. *et al.*, 1963) and the Instrumental Activities of Daily Living Scale (IADL) (Lawton M. P. *et al.*, 1969). The Neuropsychiatric inventory (NPI) was used to evaluate behavioral outcome (Cummings J. L. *et al.*, 1994). All scores were broken down by subjects having participated and

Table 1

Exclusion criteria for the study.

- Insufficient vision and hearing
- Absence of a reliable caregiver
- MMSE scores outside the range of 10-26
- Known hypersensitivity to cholinesterase inhibitors
- Evidence of other primary psychiatric or neurological disorders
- History of drug or alcohol abuse
- Unstable pulmonary, gastro-intestinal or cardio-vascular disease
- Inadequately controlled diabetes mellitus
- Thyroid disease not under control by medication
- Pre-menopauzal state
- Participation in other trials within one month of the study except DON-NY-96-003-322
- Treatment with other cholinesterase inhibitors. Other drugs were permitted.

not having participated in the previous multinational trial. Probable and possible AD patients were not entered nor analyzed separately, in order to reflect more accurately the real life prescription situation.

The statistical evaluation consisted in a descriptive analysis calculated both for the recorded data at each visit and the changes from baseline. In addition a 95% confidence interval on the mean change was calculated.

Safety was evaluated by recording the occurrence of adverse effects (AE) in all patients having received study medication. Their relationship with the ongoing study, their severity, their duration and the action taken were also evaluated. Reasons for discontinuation from the study were recorded. Safety was also assessed by physical examination and monitoring of vital signs at each visit. Clinical laboratory tests and12-lead ECG were recorded at screening and at the end of the study.

Results

Of the 200 patients enrolled, 198 subjects effectively received the study drug.

Efficacy data

The intent-to-treat efficacy (ITT) analysis was based on the data of 190 patients for whom sufficient efficacy data could be obtained. Data are given for baseline as well as for the recordings after at least 140 days of treatment.

The demographic data from the safety population and the ITT population are shown in table 2.

The changes of the mean scores of MMSE, ADLscale, IADL scale and NPI in the ITT group from baseline to end of study (after at least 140 days) are depicted in Fig. 1.

The mean change of MMSE score after at least 140 days of treatment in group I was a decrease by 0.59 points (95%CI : [-0.13 ;1.31]). For group II the mean change was an increase by 0.5 points (95%CI : [-1.26 ;0.27]). As both confidence intervals cover 0, this means that in both groups no change in MMSE score can be shown between baseline score and score after at least 140 days of treatment. In the preceding multinational trial a mean increase of MMSE score of 1.73 points had been found. This means that after 9 months of treatment the patients in group I had a mean MMSE score superior to that of the baseline of the multinational experience trial.

The mean change of ADL score after at least 140 days of treatment in group I was an increase of 0.55 points (95% CI : [-1.03 ;-0.06]). For group II the mean change was an increase by 0.61 points (95% CI : [-1.02 ;-0.20]). As both confidence intervals are situated below 0, this means that a change can be shown between baseline ADL score and score after at least 140 days of treatment.

The mean change of IADL score after at least 140 days of treatment in group I was an increase by 0.68 (95%CI : [-1.32 ;-0.03]). For group II the mean change was an increase of 0.38 points (95%CI : [-1.05 ;0.30]). On the basis of the confidence intervals, it can be concluded that only in group I a change in IADL score was found between baseline score and score after at least 140 days of treatment.

The mean change of NPI score after at least 140 days of treatment in group I was an increase of 2.33 points (95%CI : [-5.10 ;0.44]). In group II a mean change of –2.04 points was found (95%CI : [-0.21 ;4.29]). In this group significantly less patients demonstrated agitation, depression, aberrant motor behaviour and delirious ideas at the end of the study than at the starting point. However, since both confidence intervals cover 0, this implies that no change can be shown between baseline NPI score and score after at least 140 days of treatment.

Table 2

Demographic data of safety population and intent-to-treat population

	Safety population (n = 198)	Intent-to-treat population (n = 190)
Group I/Group II	74/124	72/118
Gender	68M/130F	64M/126F
Mean Age (SD)	72.3yrs (7.4)	72.2yrs (7.4)
Mean time since diagnosis	1.5 yrs (1.3)	1.5 yrs (1.2)
Mean duration of therapy (SD)		163.8 d (40.9)
Maximal dose (5 mg/10 mg)		55/135

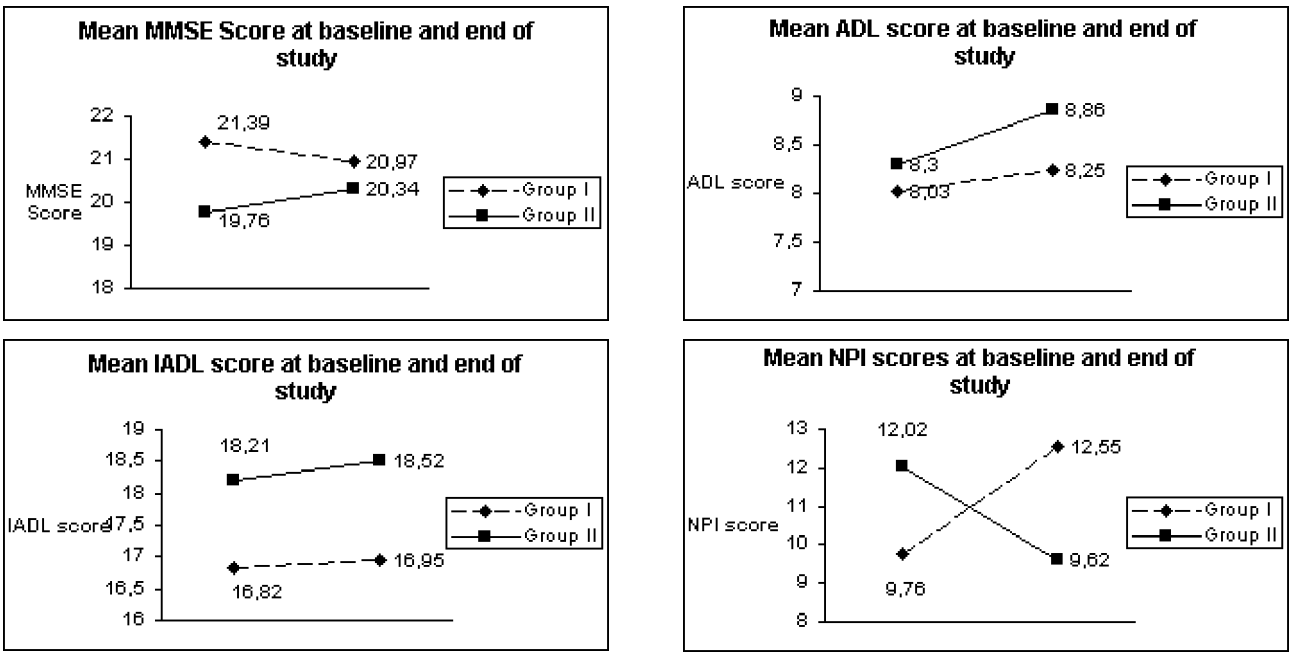

FIG. 1. — Evolution of scores for cognition, ADL and behaviour, broken down by group

SAFETY DATA

Safety data were available for all of the 198 patients who at any time received study drug. A total of 34 subjects discontinued the study prior to the final visits. Of these, only 16 (8.1%) were attributed to AE, while one patient died during the study after shock and skin ulcer. The other 17 discontinuations were due to insufficient clinical response (n = 1), adverse events (n = 16), death (n = 1), protocol violation (n = 2), lost to follow-up (n = 8), withdrawal of consent (n = 2), other reason (n = 3) or unknown reason (n = 1). For the 16 patients who left the study 26 AE were recorded (see table 3). Of all the included patients, 136 subjects (69%) suffered at least one AE. The most frequent were : nausea (n = 16, 8%),depression (n = 11, 6%), headache (n = 11, 6%), abdominal pain (n = 9, 5%), accidental injury (n = 8, 4%), bronchitis (n = 8, 4%). From all of these AE, 18 patients (9.1%) were considered as experiencing serious adverse events (SAE), many of those being accidental (Table 4). Of those SAE, 5 were considered related to the disease under study, one to concomitant treatment, and none to the investigated drug.

Discussion

In this report the results of a Belgian multicenter trial using donepezil in the treatment of mild to moderate AD are reported. There are numerous pitfalls in the interpretation of the results, mainly due to the methodology used. This was an open study, and no placebo arm was included in this trial, which makes it an observational study in many ways. Nevertheless, one of the strengths of this study is that it was performed in a very realistic setting, with the inclusion of possible as well as probable AD patients, and without stringent exclusion criteria of co-morbidity and co-medication. Therefore the observations are probably reflecting in a more accurate way the reality of the treatment of mild to moderate AD than many of the initial double-blind, placebo-controlled trials with all their restraints. The aim was not to duplicate the findings, but rather to describe and evaluate if the promises of these initial studies hold when treating patients in a routine and unselected setting.

In this context safety data were especially interesting because one can expect that in this kind of open study, occurring AE should be those observed in real life situations. The absence of a control group does not limit the importance of their occurrence, as the latter is representative of what could happen in a treated population even if a placebo effect is present. Safety results are comparable to those obtained from 2 other large studies investigating donepezil during 24 weeks (Rogers S. L. *et al.*, 1998 ; Feldman H. *et al.*, 2001). In those 2 studies, drop-out rates due to AE were 11% and 8% respectively which is very similar to the 8% found in this Belgian study. In these prior studies, SAE were reported in a proportion of 6% and 13% respectively which encompass our figure of 9.1% and were also reported, as in the present study, as mostly unrelated to donepezil. The total number of patients experiencing an AE in our study (69%) is slightly lower than the one (83%) reported in the Feldman study, but in the latter the number of AE was also quite elevated in the placebo group (80%). Aetiology of these AE are however quite similar to those reported in both other 24-week studies with

Table 3

AE that led to discontinuation (by frequency order)

	Number	%
Population	198	100
Subjects who discontinued study due to AE	16	8.08
ADVERSE EVENT		
Diarrhea	3	1.52
Vomiting	3	1.52
Dizziness	2	1.01
Headache	2	1.01
Hostility	2	1.01
Agitation	1	0.51
Anorexia	1	0.51
Anxiety	1	0.51
Chest pain	1	0.51
Confusion	1	0.51
Dry mouth	1	0.51
Dyspepsia	1	0.51
Labile blood pressure	1	0.51
Nausea	1	0.51
Nervousness	1	0.51
Pain	1	0.51
Peptic ulcer	1	0.51
Suicide attempt	1	0.51
Vertigo	1	0.51
Total	26	

Table 4

Serious AE

	Number	%
Population	198	100
Subjects who suffered a SAE	18	9,09
SERIOUS ADVERSE EVENT		
Accidental injury	2	1.01
Bone fracture(s)	2	1.01
Accidental fall and malaise	1	0.51
Arthrosis	1	0.51
Agitation and hostility	1	0.51
Bronchopneumonia	1	0.51
Confusion	1	0.51
Dehydratation, extrapyramidal syndrome and lung edema	1	0.51
Diverticulitis	1	0.51
Hostility	1	0.51
Hyperventilation	1	0.51
Shock and skin ulcer (leading to death)	1	0.51
Subdural hematoma	1	0.51
Suicide attempt	1	0.51
Syncope	1	0.51
Vomiting	1	0.51

cholinergic side-effects, especially gastro-intestinal side-effects, being the most frequent. As in these 2 other studies however, many AE were not related to the study drug but mainly to age and pre-existing conditions.

The efficacy data demonstrate that no changes occurred between baseline and end of study as far as cognition and behaviour are concerned. However, opposite trends were found in group I and group II. As mentioned above the MMSE scores of group I at the end of this trial were still superior to those at the baseline of the preceding international trial. Therefore the different trend in both groups might be considered an effect of timing, with group II demonstrating a trend more reminiscent of an initial treatment effect, as demonstrated in placebo-controlled trials. If this also applies to the findings for behaviour is unclear.

Minor deteriorations of ADL and IADL were found. The magnitude of these, however, is clinically insignificant. Therefore, we can conclude that patients remained stable over this 24-week period of open-label treatment with donepezil. This might be in contrast with other trials that have reported improvements of cognition, functional abilities as well as behaviour. However, several specific aspects of this study should be mentioned. First, as already mentioned, most of the abovementioned studies have been performed in different settings. Second, in most reports different outcome measures were studied. Third, the baseline data of our patients were relatively mild, in that most of the patients were in the mild range of deterioration. It has been described before that changes in favour of the active treatment group are larger in more severely affected, i.e. moderately severe dementia, and that this can be predicted from the natural course of AD (Santens P., 2000). The results of this study therefore might be less impressive, but confirm that during a 6-month treatment with donepezil, AD patients may remain stable on measures of cognition, behaviour and overall function.

Conclusions

This Belgian multicenter open study confirms that donepezil is safe and well tolerated and that the data on safety and efficacy obtained by robust double-blind, placebo-controlled studies can be confirmed in real life situations.

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Appendix : list of participants

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