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Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease

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Abstract

Introduction: The purpose of this study was to study the effect of donepezil on the rate of hippocampal atrophy in prodromal Alzheimer's disease (AD).

Methods: A double-blind, randomized, placebo-controlled parallel group design using donepezil (10 mg/day) in subjects with suspected prodromal AD. Subjects underwent two brain magnetic resonance imaging scans (baseline and final visit). The primary efficacy outcome was the annualized percentage change (APC) of total hippocampal volume (left + right) measured by an automated segmentation method.

Results: Two-hundred and sixteen only subjects were randomized across 28 French expert clinical sites. In the per protocol population (placebo = 92 and donepezil = 82), the donepezil group exhibited a significant reduced rate of hippocampal atrophy (APC = −1.89%) compared with the placebo group (APC = −3.47%), $P < .001$. There was no significant difference in neuropsychological performance between treatment groups.

Discussion: A 45% reduction of rate of hippocampal atrophy was observed in prodromal AD following 1 year of treatment with donepezil compared with placebo.

Keywords: Randomized controlled trial; Amnestic MCI; MRI; Volumetric imaging; Donepezil; Rate of atrophy; Hippocampus; Whole brain analysis; Alzheimer's disease; Prodromal Alzheimer's disease; Mild cognitive impairment; Biomarker; Therapy

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1. Introduction

The concept of prodromal Alzheimer's disease (AD) was recently introduced by the International Working Group on the New Criteria for the diagnosis of AD [1] to describe the stage of AD where clinical symptoms, including episodic memory disorders of the hippocampal type, are present but not sufficiently severe to impact significantly on activities of daily living and where biomarker evidence is supportive of the presence of Alzheimer pathology. Detection and identification of AD at the prodromal stage may allow delaying disease progression through appropriate treatment intervention [2]. AD phenotypical prodromes fall within the set of symptoms associated with mild cognitive impairment (MCI), a heterogeneous clinical condition that may be caused by different disorders. The use of specific memory tests, such as the Free and Cued Selective Reminding Test (FCSRT), significantly increases the capability to identify prodromal AD within the group of MCI subjects [3]. Moreover, the recall performance of the FCSRT has been significantly correlated with hippocampal volume and with cerebrospinal fluid (CSF) biomarker changes of the Alzheimer type [4,5].

In patients diagnosed with AD, either at prodromal or at dementia stages, the association between rates of brain atrophy and cognitive decline has been explored [6–8]. MCI subjects who progress to AD dementia frequently demonstrate a faster rate of hippocampal atrophy and increased ventricular expansion relative to healthy controls and subjects with stable nonprogressive MCI. Greater hippocampal atrophy has also been observed in patients with rapidly progressing AD relative to those exhibiting slower progression [6]. These results indicate a continuum of increased hippocampal atrophy as patients evolve from prodromal to mild, moderate, and severe AD dementia. Therefore, it is important to determine if subjects with amnestic MCI may experience clinical benefits, such as delayed emergence of dementia or preservation of functional activities, through treatment with interventions that have a disease modifying effect on established core biomarkers brain structure and morphology, such as hippocampal and whole brain atrophy. To answer this question, the first step is to investigate and potentially identify interventions that significantly reduce hippocampal and whole brain atrophy in a carefully characterized and selected prodromal AD target population. After the identification of such candidate treatments, it can be determined if effective early modification and prevention of atrophy may then modify the progression of clinical and functional disease related symptoms. An interrelation of neuroanatomical brain changes with the clinical phenotype of AD may well be nonlinear and is not yet fully understood and needs to be elucidated.

Donepezil hydrochloride (HCl) is a chemically unique, piperidine-based acetylcholinesterase inhibitor that has shown cognitive and functional benefit in the treatment of mild, moderate, and severe AD dementia in multiple randomized controlled trials [9]. In addition to its symptomatic effects on memory and cognition, donepezil has demonstrated some effects on the cellular and molecular system level associated with AD in nonclinical studies that may contribute to the significant changes observed on hippocampus in patients with mild moderate AD dementia treated with donepezil [10,11]. In subjects with MCI, the effect of donepezil is less clearly understood. Evidence from several large-scale clinical trials failed to demonstrate a statistically significant benefit on symptomatic outcome in this heterogeneous population [12,13]. A possible effect on brain structures in subjects with MCI is controversial with one study showing no effect on hippocampal, entorhinal cortex, whole brain, or ventricular volume [14] and another study showing a reduction in ventricular, cortical, and whole brain atrophy relative to placebo. [15]

To examine the hypothesis of a disease modifying effect of donepezil on AD-related brain structural alterations derived from the pilot trial we constructed a large-scale multicenter study. In this double-blind, randomized, placebo-controlled study in subjects with amnestic MCI, hippocampal volume was used as the primary outcome criterion to determine whether donepezil slows the progression of atrophy. Subjects with prodromal AD were isolated from the broader group of MCI subjects based on identification of an amnestic syndrome of the hippocampal type characterized by a significant impairment of memory recall that does not benefit from cueing [4,16]. In this well targeted and specific subset of MCI subjects, it was hypothesized that donepezil would decrease the rate of hippocampal atrophy relative to placebo and that this decrease would be associated with reduced decline on neuropsychological assessments.

2. Methods

2.1. Study population

The protocol of the 'Hippocampus study' and informed consent forms were approved by the Ethics Committee of Salpêtrière Hospital. A total of 332 patients were screened within the national network of Memory Resources and Research Centers (CMRR) consisting of 28 regional university expert centers with neurologists, geriatricians, neuropsychologists, biological, and neuroimaging resources in each center.

During visit 0, the clinical diagnosis of MCI was evaluated through clinical, neurological, and neuropsychological evaluation including the FCSRT, Hamilton Depression Scale, clinical dementia rating (CDR), Mini-Mental State Examination (MMSE), and Instrumental Activities of Daily Living. To be eligible for enrollment, patients should have met the following criteria: (1) more than 50 years of age; (2) a progressive hippocampal amnestic syndrome defined by free recall $\leq$17 or total recall $<$40 on the FCSRT; and (3) no dementia with a CDR stage of 0.5 and preserved cognition and functional

performance. Subjects who met the eligibility criteria were enrolled in the randomization phase beginning with visit 1.

2.2. Study design and randomization

This was a multicenter double-blind, randomized, placebo-controlled, parallel group study consisting of a 4-week selection period (visit 0) and a 12-month randomized double-blind treatment period (visit 1 to visit 4) followed by an open label extension period (visit 4 to visit 5) for a total study duration of up to 18 months (Fig. 1). At visit 1, patients underwent baseline magnetic resonance imaging (MRI) evaluation and a battery of secondary efficacy measure neuropsychological and cognitive evaluations including the Alzheimer's Disease Assessment Scale-cognitive subscale, MCI version (ADAS-COG-MCI), MMSE, Modified Isaacs test score, California Verbal Learning Test (CVLT), Trial Making Tests (TMT) A and B, and the Benton Test. After baseline evaluation, patients were randomly assigned to one group out of two, corresponding to either active treatment or placebo [one capsule of 5 mg donepezil daily for weeks 0 to 6, then two capsules of 5 mg donepezil (i.e., 10 mg) daily from week 6 to month 12 for double-blind treatment; or 1 placebo capsule daily for weeks 0 to 6, then two capsules daily from week 6 to month 12 for double-blind treatment, respectively].

Adverse events and vital signs were evaluated 6 weeks after baseline evaluations (visit 2) and at month 6 (visit 3). At month 12 (visit 4), patients underwent their second MRI evaluation along with the battery of secondary efficacy measure neuropsychological and cognitive evaluations as conducted at visit 1. Patients who withdrew after the end of month 3, but before visit 3 did not undergo an MRI but underwent all secondary efficacy measure, neuropsychological and cognitive evaluations. Patients who withdrew at or after month 6 received an MRI and underwent all secondary efficacy measure, neuropsychological, and cognitive evaluations.

2.3. Acquisition of MRI data

MRI was performed in each center with the same acquisition procedure. Patients underwent their first brain MRI scan before the baseline visit (visit 1). This scan was validated by a central reading structure. Patients underwent a second MRI scan at the final visit (defined as visit 4 at month 12 of double-blind treatment or at a time point after month 6 in case of early withdrawal).

Brain MRI scans were performed using 1.5 Tesla or 3 Tesla MRI scanners qualified by the central MRI analysis core at the Cogimage team, **Institut du Cerveau et de la Moelle épinière**, to confirm compatibility with the segmentation software to be used in the study. Equipment-related variability in MRI measurements was reduced by evaluating all patients enrolled with the same scanner at both measurements. Sequences used included 3D T1-weighted, 2D fluid attenuated inversion recovery, and 2D T2-weighted volumes of the entire brain, and a diffusion-weighted sequence.

2.4. Evaluation of MRI data

To further increase sensitivity to actual change between the two time points, hippocampal volumes were computed with a longitudinal extension of the automatic version of **Segmentation Automatique Compétitive de l'Hippocampe et de l'Amygdale** [17] software which uses information from both time points at the same time. The extension relied first on a preliminary registration of the baseline and follow-up MRI scans in a common space. Intensities of both scans were then normalized. These two preprocessing steps allowed

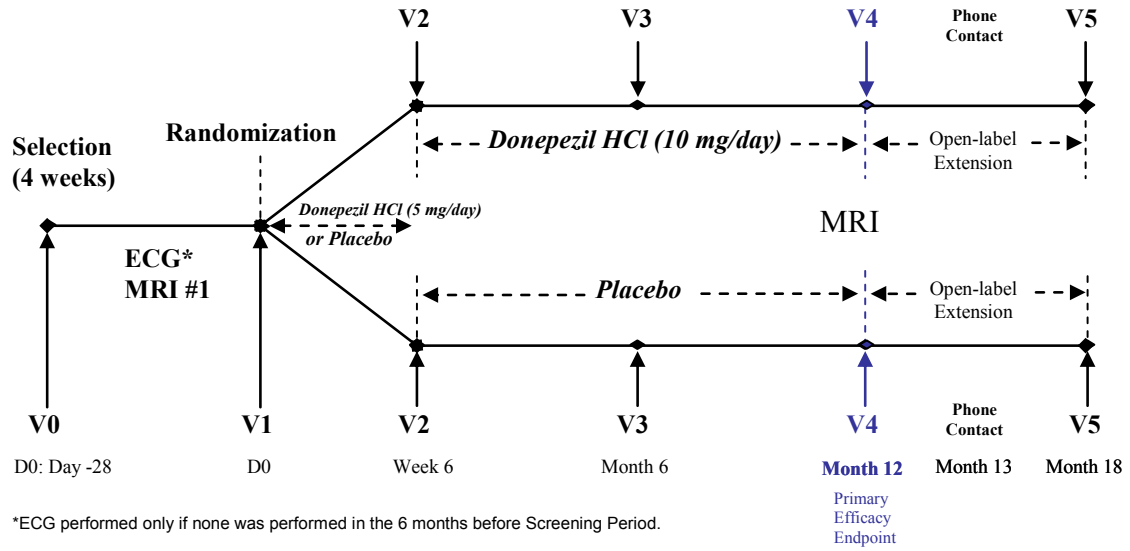

Fig. 1. Study diagram. Magnetic resonance imaging (MRI) scans were performed and validated by the central MRI analysis core before baseline and at final visit. Cognitive and neuropsychological assessments were performed at screening, randomization visit (visit 1) and month 12 (visit 4), and at premature discontinuation between months 3 and 12. At month 6 (visit 3), the Mini-Mental Status Examination (MMSE) and Alzheimer's Disease Assessment Scale–Cognitive Subscale–Mild Cognitive Impairment (ADAS-COG-MCI) tests were also performed. Safety was evaluated through patient interviews and adverse events.

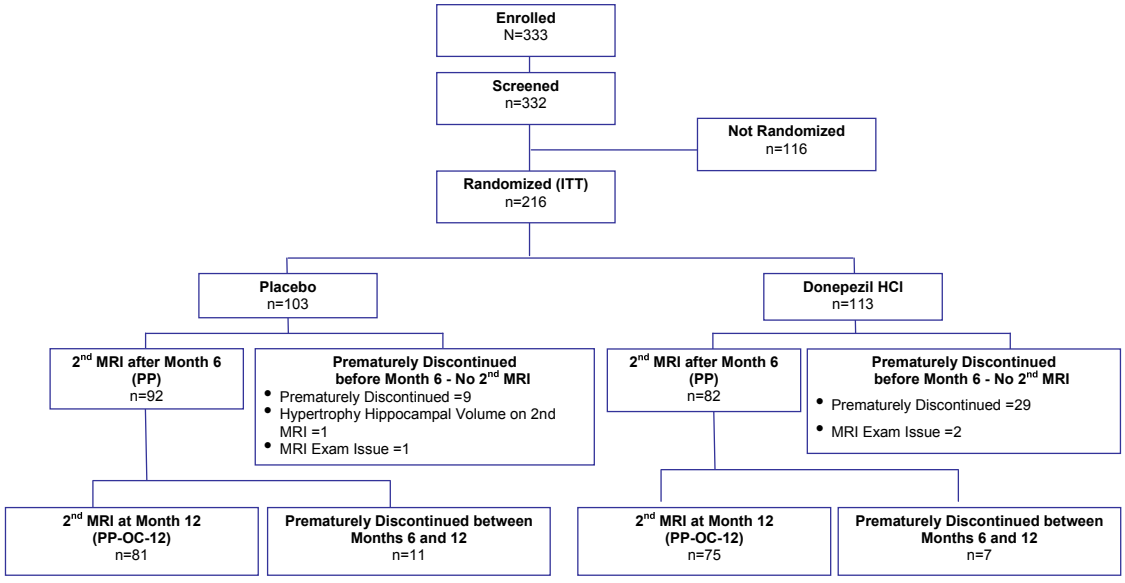

Fig. 2. Patient disposition flow chart showing the total number of patients randomized to each treatment group (ITT population); number of patients who prematurely discontinued before month 6; number of patients with a second magnetic resonance imaging (MRI) after month 6 (PP population); number of patients who prematurely discontinued between months 6 and 12, and the number of patients with a second MRI at month 12 (PP-OC-12 population). Similar proportions of patients in the donepezil and placebo groups completed the study. ITT: intent-to-treat population; PP: per protocol population; PP-OC-12: per protocol-observed case at month 12 population.

a direct comparison of both acquisitions; the same kind of preprocessing steps have already been used for longitudinal analyses (Fig. 3) [18,19]. The baseline and final visit MRI scans were first segmented jointly (i.e., considered as identical and leading to a single segmentation). The resulting segmentation was then used as an initialization of separate segmentations while keeping the two segmentations consistent between the two time-points. Taking into account both acquisitions at the same time in longitudinal analyses allows obtaining results that are more sensitive to actual change [20].

2.5. *Efficacy measures*

The primary outcome was the APC of total hippocampal volume (THV) from baseline to final visit. Secondary MRI outcomes included left and right hippocampal volume, global cerebral volume, and ventricular volume APCs from baseline to final visit. Additional secondary outcomes included the ADAS-COG-MCI, MMSE, Isaacs verbal fluency and lexical fluency tests, CVLT, TMT-Part A, and TMT-Part B and Benton test. Neuropsychological assessments were conducted in the same order and by the same evaluator at each visit to minimize variability in patient and caregiver responses. In this report, all primary and secondary outcomes were evaluated for the per protocol population, which consisted of all randomized patients who took at least one dose of study drug, had a second MRI, and did not have any major protocol deviations.

2.6. *Statistical analysis*

2.6.1. *Power analysis*

The required sample size of 100 patients per group was calculated based on primary efficacy criterion of APC in THV from baseline to final visit, with a bilateral test performed with $\alpha = 0.05$ and $\beta = 0.20$ (80% power) based on the following assumptions from data reported in Jack et al. (2004) [7]:

- An estimated standard deviation of the percentage of variation of the hippocampal formation between baseline and the last value of the patient estimated of 2.5%.
- An observed decrease of 3.3% of the hippocampal volume in MCI subjects treated with placebo (Jack et al. [2004]) [7].
- An expected decrease of 2.3% of the hippocampal volume in subjects treated with donepezil. A total of 240 patients were planned to be randomized based on an expected withdrawal rate of 20% to achieve the required 100 assessable patients per treatment group.

2.6.2. *Demographic, clinical and MRI volumetric variables*

Baseline demographic, clinical, neuropsychological, and MRI volumetric variables were compared between patient groups (placebo vs. donepezil). Fisher Exact Test was performed on categorical variables, whereas the analysis of variance (ANOVA) was used for continuous variables.

2.6.3. *Efficacy*

In this report, all efficacy criteria were evaluated using the per protocol population, defined as all randomized patients who took at least one dose of study medication, had a baseline and final visit MRI, and did not have any major protocol deviations. The primary efficacy outcome was the APC of THV from baseline to final visit. APC for primary and secondary MRI outcomes were analyzed using ANOVA. APC was computed as follows:

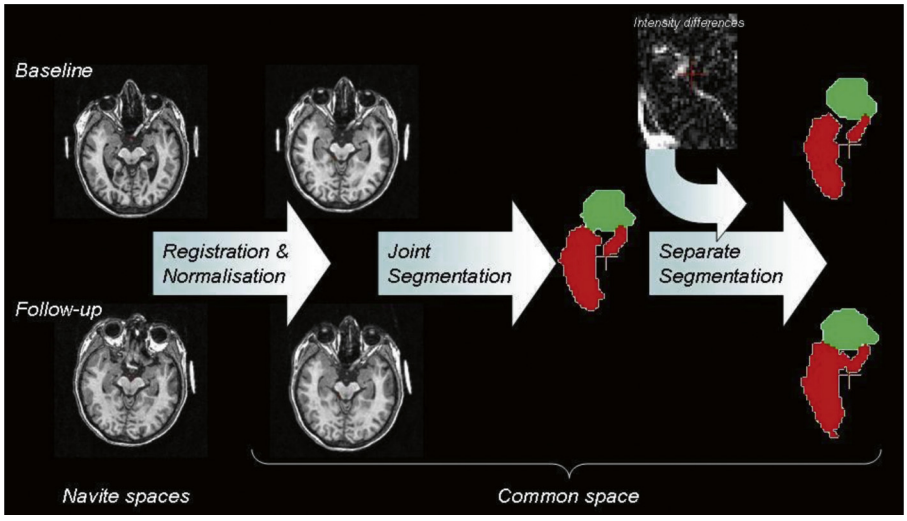

Fig. 3. Hippocampus longitudinal segmentation method illustrating preliminary registration of the baseline and final visit magnetic resonance imaging (MRI) scans in a common space followed by normalization of the intensities of both scans. The baseline and final visit MRI scans were then segmented jointly. The resulting segmentation was then used as an initialization of separate segmentations while keeping the two segmentations consistent between the two time-points.

$$APC = \frac{change\ from\ baseline}{value\ at\ baseline} \times \frac{365}{MRI\ delay} \times 100$$

Clinical and neuropsychological assessments were analyzed for the per protocol population using a change from baseline model and descriptive statistics.

2.6.4. Safety

All safety analyses were performed using the safety population comprising all randomized subjects who took at least one dose of study medication and had at least one postbaseline safety assessment.

3. Results

3.1. Study population

Of the 332 patients screened in 28 French CMRR, 216 were randomized to placebo (n = 103), or donepezil (n = 113), forming the intent-to-treat (ITT) population (Fig. 2). In the placebo ITT group, a total of 11 patients discontinued before month 6 or had MRI exclusion criteria that led to their exclusion from the per protocol population (n = 92). In the donepezil ITT group, 31 patients were excluded from the per protocol population (n = 82). A total of 11 patients in the placebo group and seven in the donepezil group discontinued between month 6 and month 12.

At the start of the double-blind treatment period (visit 1), age, sex, level of education, well-being, and cognitive ability of patients did not differ significantly between the placebo and donepezil groups (Table 1). Apolipoprotein E (*APOE*) data were available for 43 patients in the placebo group (41.7%) and 39 patients in the donepezil group (34.5%). Within these subsets, 20 (46.5%) patients in the placebo group and 23 (58.9%) in the donepezil group were *APOE* ε4 positive. No substantial differences were found in terms of *APOE* ε4 profile ($P = .279$) between the two groups of patients. There were no significant differences between the placebo and treatment groups at baseline for the hippocampal volume (total, left, or right), global cerebral volume, or ventricular volume (Table 2).

3.2. Primary outcome measures

In the per protocol population, a significant difference was observed between the treatment groups for the primary endpoint of APC in THV (Table 3) with reduced rate of atrophy observed in the donepezil group ($P < .001$). The donepezil group exhibited a slower rate of hippocampal atrophy versus placebo over a 1-year period for the per protocol population (APC = -1.89% [SE = 0.34] vs −3.47% [SE = 0.32], respectively, n = 174, $P < .001$). The results showed a difference of 1.58 percentage points (size effect) of hippocampal volume APC (N = 92 and 82 for the placebo group and donepezil group, respectively). Considering only the sample of patients who performed MRI at 12 months, the donepezil group showed again a significant reduced rate of hippocampal atrophy (APC = −1.78%) compared with the placebo group (APC = −3.08%, $P = .02$) of the same amplitude with a size effect of 1.30 percentage points.

No significant difference was found comparing APC in THV between placebo and donepezil *APOE* ε4 carriers ($P = .424$.)

3.3. Secondary outcome measures

Significant differences were observed between placebo and donepezil groups for all secondary MRI outcome measures in the per protocol population (Table 3). APC of both left and right hippocampal volumes demonstrated significantly reduced atrophy in the donepezil treatment group relative to the placebo group (−1.81% vs −3.64%,

Table 1
Screening and baseline demographic and patient characteristics: ITT population

	Placebo (n = 103)	Donepezil (n = 113)	*P*-value
Screening characteristics			
Duration of memory disorders (months)			.175
N	103	113	
Mean (SD)	33.02 (25.30)	37.98 (28.09)	
Free recall			.281
N	103	113	
Mean (SD)	11.34 (5.55)	12.14 (5.34)	
Total recall			.359
N	103	113	
Mean (SD)	29.65 (9.78)	30.82 (8.96)	
Baseline characteristics			
Age, years, mean ± SD	73.67 ± 6.61	74.13 ± 6.40	.607
Sex			1.000
Male (%)	49 (47.6)	54 (47.8)	
Female (%)	54 (52.4)	59 (52.2)	
APOE genotype, positive for *APOE* ε4			.279
n (%)	20 (46.5)	23 (58.9)	
Missing	60	74	
Education, n (%)			.096
No schooling	1 (1.0)	0 (0.0)	
Primary	7 (6.8)	9 (8.0)	
Certificate of primary education	47 (45.6)	44 (39.3)	
Secondary (baccalaureate)	17 (16.5)	34 (30.4)	
Higher education	31 (30.1)	25 (22.3)	
Missing	0	1	
Hamilton Rating Scale for Depression			.488
n/N	58/103	72/113	
Mean (SD)	3.05 (2.82)	2.72 (2.57)	
ADAS-COG-MCI			.563
n/N	103/103	113/113	
Mean (SD)	12.20 (4.22)	11.87 (4.18)	
MMSE			.420
n/N	103/103	113/113	
Mean (SD)	25.83 (2.57)	26.09 (2.21)	

Abbreviations: SD, standard deviation; *APOE*, apolipoprotein E; ITT, intent-to-treat; ADAS-COG-MCI, Alzheimer's Disease Assessment Scale-cognitive subscale, MCI version; MMSE, Mini-Mental State Examination.

NOTE. *P*-value denotes a significant difference at the Fisher Exact Test and the analysis of variance for categorical and continuous variables, respectively.

$P = .001$ and −2.02% vs 3.45%, $P = .008$, respectively). In addition, both APC of global cerebral volume and APC of ventricular volume differed significantly between placebo and donepezil groups (−0.71% vs −0.41% $P = .005$ and 4.87% vs 3.16%, $P < .001$, respectively). *APOE* ε4 carriers of both groups showed the same APC in the right, left hippocampus ($P = .743$ and $P = .339$, respectively) and in the global cerebral and ventricular volumes ($P = .181$ and $P = .239$, respectively).

Finally, the neuropsychological scores at baseline did not reveal any significant difference between the placebo group and the donepezil treatment group for each neuropsychological test (ADAS-COG-MCI, MMSE, Isaacs verbal and lexical fluency tests, CVLT total score, TMT A and B, and the Benton Test) in the per protocol population.

Table 2
Baseline volumetric measures (cubic centimeters) per protocol population

	Placebo (n = 92)	Donepezil (n = 82)	*P*-value
Total hippocampal volume			.743
n/N	92/92	82/82	
Mean (SD)	4.84 (0.88)	4.88 (0.84)	
Left hippocampal volume			.753
n/N	92/92	82/82	
Mean (SD)	2.37 (0.47)	2.35 (0.47)	
Right hippocampal volume			.350
n/N	92/92	82/82	
Mean (SD)	2.47 (0.48)	2.53 (0.44)	
Global cerebral volume			.862
n/N	92/92	80/82	
Mean (SD)	980.33 (108.64)	983.21 (107.94)	
Ventricular volume			.916
n/N	92/92	80/82	
Mean (SD)	52.10 (18.74)	51.79 (20.25)	

NOTE. *P*-value denotes a significance difference at analysis of variance.

3.4. Adverse events

Overall, the number of patients experiencing treatment emergent adverse events (TEAEs) was higher in the donepezil treatment group (88 patients; 77.9%) relative to the placebo group (67 patients; 65.0%). A total of 32 patients in the donepezil group (28.4%) experienced TEAEs considered serious or severe, compared with 18 (17.5%) in the placebo group. Discontinuations due to TEAEs also occurred at higher frequency in the donepezil treatment group (20 patients; 17.7%) compared with the placebo group (seven patients; 6.8%). The most common TEAEs (>5%) that occurred with greater frequency in the donepezil group included muscle spasms, nightmares, diarrhea, headache, nausea, sleep disorder, abdominal pain, and vertigo. Adverse events reported in the study are in relation with the cholinergic properties of the drug and were expected at the notable exception of the pyrexia. They were observed at the same rate and in the same proportion than in the existing literature except for muscle spasms that were more frequent. No death has been recorded during the overall length of the study period.

4. Discussion

This large-scale, randomized, double-blind, multicenter study demonstrates a statistically significant reduction of 45% in the APC of THV in a selected subgroup of MCI subjects on 10 mg/day of donepezil. The donepezil HCl group exhibited a slower rate of hippocampal atrophy versus placebo over a 1-year period for the per protocol population (APC = −1.89% [SE = 0.34] vs −3.47% [SE = 0.32], respectively, n = 174, $P < .001$). These findings were maintained also in the subsample of patients who had their second MRI at 12 months. Secondary neuroimaging efficacy

Table 3
APC in volumetric measures (%) in per protocol population

	Placebo (n = 92)	Donepezil (n = 82)	Treatment difference (95% CI)	*P*-value
APC of total hippocampal volume			−1.58 (−2.51, −0.65)	$P < .001$
n/N	92/92	82/82		
Mean (SE)	−3.47 (0.32)	−1.89 (0.34)		
APC of left hippocampal volume			−1.83 (−2.94, −0.71)	$P = .001$
n/N	92/92	82/82		
Mean (SE)	−3.64 (0.39)	−1.81 (0.41)		
APC of right hippocampal volume			−1.43 (−2.47, −0.38)	$P = .008$
n/N	92/92	82/82		
Mean (SE)	−3.45 (0.36)	−2.02 (0.39)		
APC of global cerebral volume			−0.30 (−0.51, −0.09)	$P = .005$
n/N	92/92	80/82		
Mean (SE)	−0.71 (0.07)	−0.41 (0.08)		
APC of ventricular volume			1.71 (0.75, 2.67)	$P < .001$
n/N	92/92	80/82		
Mean (SE)	4.87 (0.33)	3.16 (0.35)		

Abbreviations: APC, annualized percentage change; SE, standard error.
NOTE. *P*-value denotes a significant difference at analysis of variance.

parameters also showed significant differences between treatment groups in favor of the donepezil group for the left hippocampal volume APC ($P = .001$), the right hippocampal volume APC ($P = .008$), the global cerebral volume APC ($P = .005$), and the ventricular volume APC ($P < .001$). Moreover, there was no effect of *APOE* ε4 status on any these MRI measures. No significant difference between treatment groups was observed in any of the neuropsychological tests. Adverse events in the donepezil 10 mg/day group consisted mainly of expected acetylcholinesterase inhibitor effects including abdominal pain, sleep disorders, nausea, and diarrhea.

Previous studies have shown some evidence of structural changes in the brain of AD patients under donepezil. A small decrease in left hippocampal volume was reported after 24-week of donepezil compared with the placebo-treated subjects in a randomized double-blind, placebo-controlled monocenter study [10]. More recently, a randomized, double-blind placebo-controlled monocenter study reported significant differences favoring the donepezil group for cortical region and whole brain volumes although the primary MRI outcome measure HC volumes was statistically nonsignificant [15]. In contrast to the current study, the former two pilot studies none of these studies was performed in a large-scale community-based multicenter cohort and subjects were not included on the basis of the FCSRT, a memory test that was reported to be correlated with hippocampal volume and CSF changes of the Alzheimer type [4,5].

Our results obtained on the primary structural outcome despite enrollment of less than 120 patients/treatment arm may be explained by selection of a specific study population and sensitive and highly controlled measurement of hippocampal volume. The selection of MCI subjects with an amnestic syndrome of the hippocampal type (defined by a low free score not normalized with cueing at the FCSRT) identifies the right target population (i.e., prodromal AD patients) with a high specificity because it assesses verbal episodic memory with semantic cueing that allows one to control for encoding and to facilitate retrieval to isolate the storage capacities of the patients. In addition, the use of stringent cutoff scores (free recall below $\leq$17 or a total recall score below $<$40) permitted specific selection of MCI progressors who may convert to dementia in a short period of time.

For the first time to our knowledge, the rate of hippocampal atrophy was the primary outcome of a large-scale community based multicenter clinical trial in prodromal AD. Hippocampal volume was chosen for several reasons: (1) it is central to the pathophysiology of AD as it is one of the earlier and more severely affected regions in AD; (2) it is well delimited with rather well-defined boundaries, validated, localized, and central to the neurodegenerative pathophysiology. This region can be analyzed with 3D-MRI.

Another strength of the study is that it was performed in a single country. This significantly reduced the variability of the data and also facilitated a centralized neuroimaging network with a centralized reading for MRI quality and analysis of images supervised by a single investigator. The choice of an automated segmentation method for assessing hippocampal volume also decreased human intervention compared with manual segmentation. This allows more sensitive volume measures to be obtained because it reduces variability caused by noise and position differences. This procedure provides a high reproducibility and it is specifically adapted for longitudinal studies with for repeated investigations. All these controls may have contributed the strong statistical effect of donepezil on hippocampal rate of atrophy.

Despite the highly significant effect on hippocampal atrophy, no significant difference between treatment groups was observed in the cognitive evaluations for the Per Protocol and ITT populations. It should be noted, however, that the patients were at very mild stage of the disease as expected based on the inclusion criteria (with a mean score of 11.87 at the ADAS-COG at baseline in the treated group, see Table 1) indicating that their cognitive problems were mostly restricted

to memory disorders. Furthermore, it has been demonstrated that the number of patients per arm necessary to detect a given effect based on hippocampal atrophy rate is much smaller than that needed to detect the same effect based on cognitive assessment variations [21]. The absence of clinical relevance and of significant changes on the neuropsychological performance of the structural effect prevents us to conclude to any disease modifying effects of the donepezil in prodromal AD.

Some limitations of the present study should also be considered. The protocol of the study did not include information on the settings of the subjects of the population or on race and ethnicity characteristics or data in terms of lifestyle. The latter, in particular, with its practical aspects—nutrition, hydration, alcohol consumption, smoking, and physical activity—has become significant in terms of AD prevention [22]. Although it is most likely that these factors were matched between the two groups of patients, further studies are needed to elucidate the impact of these factors in the prodromal or even in the asymptomatic stages of AD. We should also mention the number of drop-outs and the lack of *APOE* data on the entire group as potential limitations of the study.

In summary, our study showed a 45% reduction of the rate of hippocampal atrophy after one of treatment with donepezil in patients suspected to have prodromal AD. The result was obtained in a relatively small number of patients, underlying the interest of a well-selected population and centralized procedures. This is the first large-scale multicenter study of a treatment in subjects with MCI to show a positive result for a biological (morphological) primary efficacy variable. This is also the first time that a statistically significant effect of a drug is reported on rate of hippocampal atrophy in subjects with MCI. The clinical significance of this result is unclear and additional research will be needed to determine if the specific subset of MCI subjects with prodromal AD will benefit from donepezil treatment as a preventive measure to maintain memory and autonomy. Longer observation periods and longitudinal studies are warranted to evaluate the association between reduced rate of hippocampal atrophy and protective effects on cognition, such as memory and other clinically relevant domains.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources. A stabilization of cognitive changes was reported in a few studies in patients with mild cognitive impairment (MCI) treated with donepezil. Only two studies have challenged a potential disease-modifying effect of donepezil in subjects with MCI, none of these showing a significant effect on specific brain structures.
2. Interpretation: Several features may account for the reduction of 45% in the rate of hippocampal atrophy reported here: the population chosen (amnestic MCI), the structure chosen (hippocampus), the method chosen (automated segmentation), and the procedures chosen that decreased variability (one country, a centralized neuroimaging network …). Besides these elements, the question of a specific effect of donepezil on AD brain lesions is raised.
3. Future direction: There is a need to replicate the results in prodromal AD to understand the basic mechanism through which donepezil impact morphology and/or structure of brain regions affected by AD.

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