The Effects of Donepezil on Alzheimer's Disease Progression Monitored by MRI

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STUDY OVERVIEW

INTRODUCTION

- Amnestic mild cognitive impairment (aMCI) is defined as a significant impairment in memory with slight or no impairment in activities of daily living.[1]
- As many as 80% of patients with aMCI progress to Alzheimer's disease (AD) within 6 years of diagnosis.[1]
- Donepezil has been shown to delay progression to AD over a period of 1 year[2] and to significantly improve modified Alzheimer Disease Assessment Scale-cognitive subscale (mADAS-cog) scores.[3]
- Donepezil has also been shown in magnetic resonance imaging (MRI) studies to reduce rates of hippocampal atrophy in patients with AD.[4-7]
- This study was designed to seek evidence for disease-modifying effects of donepezil in patients with aMCI, based on brain volumetric analysis.

OBJECTIVES

- To evaluate the effect of donepezil on the rate of atrophy of the hippocampus, entorhinal cortex, whole brain, and ventricles, as assessed by change in volume.
- To assess the correlation of brain volumes with clinical assessment measures.

CONCLUSIONS

- **Donepezil treatment was associated with small but significant improvements in mADAS-cog scores, but not CDR-SB scores.**
- **Donepezil treatment was associated with improvement on subjective patient measures.**
- **There were no statistically significant effects of donepezil on hippocampal, entorhinal, or whole brain atrophy volumes, change in the brain volumes, or percent change in the brain volumes per year.**
- **Weak but significant correlations were observed between declining cognition and smaller hippocampal, entorhinal, and whole brain atrophy volumes.**
- **These preliminary brain volumetric analyses showed a high degree of variability, which likely affected the results; further analyses are ongoing to explain the variance.**

RESULTS

- Preliminary results are presented; final analyses are ongoing.
- A total of 409 patients were randomized to donepezil and 412 to placebo; 379 on donepezil and 378 on placebo were included in the intent-to-treat (ITT) population.
- Of the patients included in the ITT population, 110 patients treated with donepezil and 119 patients treated with placebo had baseline and repeat MRIs at the predefined times (MRI-ITT population).
- The treatment groups had baseline characteristics comparable to the treatment groups of the overall study, and the treated and untreated patients in the MRI subpopulation had similar baseline characteristics (Table 1).

Efficacy Outcomes

- Donepezil improved mADAS-cog scores but had no effect on CDR-SB scores in the ITT population of the parent study (Table 2).
  - Donepezil had no statistically significant effect on secondary efficacy measures, except for an improvement in PDQ and PGA scores.
- There were no statistically significant differences between donepezil and placebo in the change in hippocampal, ERC, and whole brain atrophy volumes (Table 3) or the percent change in these brain volumes per year (Table 4).
  - The results were highly variable; analyses are ongoing to explain the variance.
- Correlations between brain volumes and clinical assessments at both baseline and study end point and between the percent rate of change in brain volumes per year and the change in clinical assessments were performed on the combined treatment groups (Table 5).
  - There were weak, but statistically significant, correlations of all measured brain volumes with mADAS-cog scores at baseline and at study end point.
  - There were similar correlations for 6 of the 9 measured brain volumes with CDR-SB scores at study end point, but there was no correlation at baseline.
  - In general, there were no correlations of the percent rate of change in brain volumes per year with changes in either mADAS-cog scores or CDR-SB scores.
- Treatment differences in brain volumes and correlations between brain volumes and clinical assessments generally were unaffected by *APOE* genotype or by head-size adjusted brain volumes. The exceptions were:
  - A significant treatment difference between donepezil and placebo in head-size adjusted left ERC volume ($P = .041$)
  - A significant correlation of head-size adjusted left ERC volume and CDR-SB at end point ($P = .041$)
  - A loss of a significant correlation of hippocampal volumes and CDR-SB at end point in patients with a negative *APOE* genotype.

Table 1. Demographic and Patient Characteristics.

	MRI-ITT Population			Safety Population	
	Placebo n = 119	Donepezil n = 110	Total N = 229	Placebo n = 387	Donepezil n = 391
Age, years, mean ± SD	68.7 ± 10.1	69.8 ± 9.8	69.2 ± 10.0	69.8 ± 10.3	70.2 ± 9.7
Years since onset, mean ± SD	4.2 ± 2.2	4.5 ± 2.8	4.4 ± 2.5	4.2 ± 2.8	4.1 ± 2.4
Sex, % male	58.0	52.7	55.5	57.4	51.7
Race, white, n (%)	106 (89.1)	103 (93.6)	209 (91.3)	330 (85.3)	346 (88.5)
APOE genotype, negative, n (%)	66 (61.7)	55 (55.0)	121 (58.5)	117 (41.9)*	108 (41.2)*
Education, n (%)					
0-7 years	1 (0.8)	1 (0.9)	2 (0.9)	3 (0.8)	2 (0.5)
8-15 years	50 (42.0)	57 (51.8)	107 (46.7)	210 (54.3)	201 (51.4)
> 15 years	68 (57.1)	52 (47.3)	120 (52.4)	174 (45.0)	188 (48.1)
Baseline MMSE ≤ 28, n (%)	73 (61.3)	72 (65.5)	145 (63.3)	322 (83.2)	328 (83.9)

*$n_{placebo} = 279$; $n_{donepezil} = 262$. Apolipoprotein E4 genotyping was introduced as a protocol amendment after the start of the study. The test, though scheduled for Week -3, was also allowed at any other visit or at an unscheduled visit if necessary.

Table 2. Baseline and Change From Baseline mADAS-cog and CDR-SB Scores (ITT Population).

	Baseline		Change From Baseline		
	Placebo n = 378	Donepezil n = 379	Placebo n = 37	Donepezil n = 3798	*P**
mADAS-cog	18.2 ± 7.0	18.3 ± 6.6	-0.13 ± 0.4	-1.0 ± 0.4	.01
CDR-SB	1.5 ± 0.9	1.5 ± 0.9	0.1 ± 0.1	0.0 ± 0.1	NS

Values are mean ± SD.
**P* value for the between-groups comparison of least squares mean change from baseline.

Table 3. Effect of Donepezil vs Placebo on Change From Baseline in Brain Volumes (mm^3).

	Baseline*		Change From Baseline†		Treatment Difference	
Volume	Placebo	Donepezil	Placebo	Donepezil	(95% CI)	*P*
Total hippocampal	4059 ± 860 (117)	3938 ± 754 (110)	-65 ± 27	-63 ± 28	8 (-50 to 67)	.779
Left hippocampal	2005 ± 447 (117)	1937 ± 370 (110)	-37 ± 16	-27 ± 16	13 (-20 to 47)	.439
Right hippocampal	2054 ± 446 (117)	2001 ± 420 (110)	-28 ± 16	-36 ± 16	-5 (-39 to 29)	.779
Total ERC	1106 ± 429 (109)	1090 ± 480 (101)	-22 ± 24	-67 ± 24	-42 (-93 to 8)	.098
Left ERC	549 ± 220 (109)	548 ± 249 (101)	-6 ± 14	-35 ± 14	-28 (-57 to 0.2)	.052
Right ERC	557 ± 239 (109)	541 ± 262 (101)	-16 ± 14	-32 ± 14	-14 (-43 to 15)	.343
Total whole brain atrophy	1,195,860 ± 139,933 (105)	1,196,276 ± 159,378 (105)	5144 ± 1992 (86)	6570 ± 2145 (75)	1166 (-3060 to 5392)	.586
Ventricular region	39,049 ± 28,561 (105)	38,927 ± 21,084 (105)	1710 ± 335 (100)	1725 ± 369 (89)	30 (-718 to 778)	.937
Cortical region	1,156,811 ± 133,996 (105)	1,157,349 ± 157,934 (105)	3745 ± 1770 (86)	4871 ± 1906 (75)	925 (-2830 to 4680)	.627

*Mean ± SD (n).
†Mean ± SE (n, where different from baseline n).

Table 4. Effect of Donepezil vs Placebo on Percent Change in Brain Volumes per Year.

		Percent Rate of Change per Year*			Treatment Difference	
Volume	n	Placebo	n	Donepezil	(95% CI)	*P*
Total hippocampal	117	-1.42 ± 0.71	110	-1.68 ± 0.74	-0.08 (-1.62 to 1.46)	.921
Left hippocampal	117	-1.84 ± 0.85	110	-1.42 ± 0.89	0.63 (-1.22 to 2.47)	.504
Right hippocampal	117	-0.90 ± 0.82	110	-1.92 ± 0.86	-0.85 (-2.62 to 0.93)	.348
Total ERC	109	-0.69 ± 2.12	101	-3.84 ± 2.15	-2.93 (-7.36 to 1.51)	.195
Left ERC	109	0.64 ± 2.45	101	-4.26 ± 2.48	-4.72 (-9.85 to 0.41)	.071
Right ERC	109	-1.05 ± 2.48	101	-2.81 ± 2.52	-1.49 (-6.69 to 3.70)	.571
Total whole brain atrophy	86	0.4 ± 0.16	75	0.6 ± 0.18	0.1 (-0.2 to 0.5)	.487
Ventricular region	100	4.5 ± 0.81	89	4.2 ± 0.89	-0.5 (-2.3 to 1.3)	.617
Cortical region	86	0.3 ± 0.15	75	0.4 ± 0.16	0.1 (-0.2 to 0.4)	.494

100([end value-baseline value]/baseline value)*365.25/(end date-baseline date), mean ± SE.

Table 5. Correlation Between Brain Volumes and Clinical Assessments.

		Baseline		Study End Point		% Rate of Change per Year	
Volume	Statistic*	mADAS-cog	CDR-SB	mADAS-cog	CDR-SB	mADAS-cog	CDR-SB
Total hippocampal	SC	-0.376	-0.048	-0.416	-0.172	-0.116	-0.115
	P	< .001	.473	< .001	.010	.082	.084
Left hippocampal	SC	-0.405	-0.068	-0.447	-0.179	-0.060	-0.072
	P	< .001	.310	< .001	.007	.369	.278
Right hippocampal	SC	-0.330	-0.033	-0.356	-0.155	-0.133	-0.123
	P	< .001	.623	< .001	.019	.045	.064
Total ERC	SC	-0.214	-0.073	-0.261	-0.164	-0.085	-0.160
	P	.002	.293	< .001	.018	.221	.020
Left ERC	SC	-0.198	0.101	-0.281	-0.113	-0.074	-0.127
	P	.004	.144	< .001	.103	.288	.066
Right ERC	SC	-0.201	-0.049	-0.219	-0.173	-0.112	-0.146
	P	.003	.479	.001	.012	.107	.034
Whole brain atrophy	SC			0.235	0.080		
	P			.003	.316		
Ventricular region	SC			0.264	0.190		
	P			< .001	.009		
Cortical region	SC			0.189	0.049		
	P			.016	.537		

*SC, Spearman's correlation coefficient.
Number of subjects: hippocampal, n = 227; ERC, n = 211 (baseline), n = 210 (end point and % rate of change/year); whole brain atrophy, n = 161; ventricular, n = 189; cortical, n = 161.

METHODS

Study Design

- A brain volumetric analysis substudy of a randomized, double-blind, parallel-design trial conducted at 74 centers in the United States with a 3-week placebo run-in period followed by a 48-week double-blind period.

Study Entry Criteria

- Subjects were ambulatory or ambulatory-aided, aged 45 to 90 years, with aMCI as diagnosed by:
  - Global Clinical Dementia Rating (CDR) score equal to 0.5 at screening with the Memory Box score of 0.5 or 1.0.
  - Mini-Mental State Examination (MMSE) score of 24 to 30 inclusive.
  - A maximum score of 8 on the Logical Memory II Delayed Paragraph Recall subtest of the Wechsler Memory Scale-Revised for those with > 15 years of education, 4 for 8 to 15 years of education, and 2 for 0 to 7 years of education.
  - Rosen modified Hachinski Ischemia scale score ≤ 4.
- Subjects were excluded if they had:
  - AD or other dementia; other medical, psychiatric, or neurologic disorders that could impair cognition.
  - Drug or alcohol abuse or dependence within the last 5 years.

Protocol

- During the double-blind period, patients received either donepezil (5 mg/d for 6 weeks followed by 10 mg/d) or placebo.
- MRI was performed at baseline and Week 50 (± 7 days), as well as on subjects who terminated early but received ≥ 6 months of treatment.

Efficacy Measurements

- Clinical assessment measures were the mADAS-cog and the CDR-Sum of Boxes (CDR-SB).
  - Secondary efficacy measures in the parent study were the MMSE, Symbol Digit Modalities Test (SDMT), Digit Span Backwards test, Neuropsychiatric Inventory (NPI), Perceived Deficits Questionnaire (PDQ), Perceived Deficits Questionnaire for Relatives (PDQ-R), AD Cooperative Study Clinical Global Impression of Change-Mild Cognitive Impairment (CGIC-MCI), and the Patient Global Assessment (PGA).
- Brain volumes were analyzed from structural MRI scans ($1.0 \times 1.0 \times 1.5$ mm resolution) that were sent from investigators to Synarc Inc. (San Francisco, CA, USA) and analyzed by the Center for Imaging of Neurodegenerative Diseases (CIND, University of California and VA Medical Center, San Francisco, CA, USA), using procedures that assured the quality and standardization of both the MRI acquisition and the volume assessments.
- Brain volumes studied were left, right, and total hippocampal volumes and left, right, and total entorhinal cortex (ERC) volumes.
- Atrophy of the whole brain and of the ventricular and cortical regions was determined by the change (decrease) in volume from their respective baseline measurements.
- Correlations between brain volumes and mADAS-cog and CDR-SB scores were investigated in patients who had both MRI and clinical assessments performed.

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