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# Efficacy of acetyl-cholinesterase-inhibitor (ACHEI) treatment in Alzheimer's disease: A 21-month follow-up "real world" study

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ABSTRACT

Long-term efficacy of acetyl-cholinesterase-inhibitor (ACHEI) treatment in mild-to-moderate Alzheimer's disease (AD) is of great relevance for clinical routine and has been investigated over a 21-month period of treatment in a "real word" population. We investigated cognitive (mini mental state examination = MMSE) and functional (instrumental activities of daily living = IADL; activities of daily living = ADL) outcomes in 427 AD patients throughout the above period. At the end of the study, first-time drug takers (naives) declined by 1.2 MMSE points, whereas non-naives by 3.8 points. Predictors of responsiveness for first-time drug takers were MMSE score at baseline and MMSE points gained at 3 months of treatment. Further investigations are needed to shed light on the characteristics of responsiveness to a tailored ACHEI treatment for dementia.



## 1. Introduction

ACHEI components, such as donepezil (Geldmacher, 2004; Benjamin and Burns, 2007), rivastigmine (Onor et al., 2007) and galantamine (Villarroya et al., 2007) are recommended as first-line treatment options for patients with mild to moderate AD (Hogan et al., 2007; Waldemar et al., 2007). The benefits are symptomatic and the employment of ACHEI slows the natural course of the disease to 1 year (Mohs et al., 2001; Winblad et al., 2001).

According to systematic (Lanctot et al., 2003b) and Cochrane reviews (Birks et al., 2000; Loy and Schneider, 2004; Birks and Harvey, 2006), the efficacy of ACHEI is modest, not long-lasting, and still debatable (Lemstra et al., 2007). Birks and Harvey (2006) revised 16 randomized controlled trials (RCTs) showing that donepezil improved the cognitive functions in both 5 and 10 mg/day after 24 weeks, about 1.5 points on the MMSE versus placebo groups, and in 10 mg/day after 52 weeks (about 2 points on MMSE). Responsiveness to treatment was largely variable: 40–50% of patients taking donepezil showed a moderate improvement in their cognitive functions, whereas 15–21% of patients had greater benefits (Cummings, 2003).

Galantamine and rivastigmine-based treatment (Hogan and Patterson, 2002) showed similar results. Birks et al. (2000) examined eight RCTs employing rivastigmine and concluded that it improved cognition during a 26-week-long treatment; highlighting thus the need for a further insight, in order to clarify benefits of longer treatment periods.

ACHEI treatment demonstrated beneficial effects on ADL as well. Different measures have been used to assess functional decline. Burns et al. (1999) showed a slowing of functional decline in patients taking donepezil (using IADL and ADL), and other studies (Birks and Harvey, 2006) showed functional benefits over a period of 52 weeks of treatment using the progressive deterioration scale (PDS). Furthermore, beneficial effects have been evaluated on behavioral disturbances, such as depression, agitation, delusion and apathy (Wynn and Cummings, 2004).

Only a few studies have investigated long-term efficacy of ACHEI treatment in AD patients. A 2-year open-label study conducted by Winblad et al. (2006) following 1 year RCT, showed greater benefits of early treatment. Donepezil-treated patients over 3-year time tended to maintain preserved levels of their cognitive and functional abilities compared to those who started taking drugs at a later stage (4.9 points versus 6.2 points on MMSE). An open-label study following a 2-year RCT conducted by Farlow and Lilly (2005) showed that cognitive decline is delayed by nearly 1 year. These authors assessed the cognitive decline using ADAS-cog (Alzheimer's Disease Assessment Scale—cognitive subscale; Rosen et al., 1984), a multi-item test battery that examines memory, attention, praxis, reason, and language (score range is from 0 to 70, with higher scores indicating greater cognitive impairment). Patients lost 4 points at ADAS-cog at 84th week of treatment.

Recently Wallin et al. (2007) published the outcomes of a 3-year long donepezil-based treatment in a routine clinical setting

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showing a mean change from baseline of 3.8 for MMSE and 8.2 for ADAS-cog.

Other results concerning long-term efficacy of ACHEI treatment for dementia come from observational studies. A wide range of evidence from cohort/observational studies helps us to understand better the efficacy in the "real world". Randomized, controlled trials are referred to as the "gold standard" to prove the efficacy, due to good methodology and rigorous criteria (Tinklenberg et al., 2007). But the strict recruitment criteria of patients do not allow large generalization of results towards the rest of the clinical population ("real world"). In September 2000, the Italian Ministry of Health enacted the CRONOS project; its main purpose was the free provision of ACHEI drugs to AD patients, as long as they were diagnosed by one of the dedicated units (about 500), identified as Unità di Valutazione Alzheimer (Evaluating Alzheimer's Special Care Units). In the contest of this national project some results have been published. Bellelli et al. (2005) showed that at 9 months of ACHEI treatment only naive patients improved, whereas non-naives decreased their MMSE score. Raschetti et al. (2005) showed that at 9-month improvement was restricted to those patients who were good responders at 3 months. Sinforiani et al. (2003) reported that around 45% of patients responded well to the treatment, but no factor emerged as significant predictor of responsiveness.

The main aim of this study was to investigate the effectiveness of the ACHEI treatment (donepezil and rivastigmine) over a 21-month period. The second aim was the identification of clinical variables that can be useful in predicting responsiveness to ACHEI.

## 2. Materials and methods

### 2.1. Subjects and treatments

Outpatients ($n = 427$) diagnosed as having probable or possible mild-to-moderate AD, according the NINCDS-ADRDA criteria (McKhann et al., 1984) were consecutively enrolled in the CRONOS project at the Evaluating Alzheimer's Special Care Units of the IRCCS Centro S. Giovanni di Dio FBF (Brescia, Italy). Patients were diagnosed with AD according to clinical and neurological examinations, neuro-imaging data (CT or MRI) and neuropsychological tests.

Socio-demographic and clinical data were obtained from baseline interviews (such as, age, gender, education, previous ACHEI therapy, comorbidity and CNS-acting drugs). Cognitive functioning was measured with MMSE score (Folstein et al., 1975). Functional status was evaluated with IADL score (0–8, where 0 stands for full autonomy in instrumental activities of daily living) and ADL (0–6, where 0 stands for no deficit in basic activities of daily living). Patients were evaluated at the baseline, and after 3, 9, 15 and 21 months from baseline.

Patients allocated to donepezil-based treatment (5 or 10 mg/day) were 336, whereas 91 received rivastigmine (from 3 to 12 mg/day). Allocation to treatment has been done by the physician, on the basis of patients' clinical history and features.

According to the rules delivered by the Italian Ministry of Health, treatment had to be discontinued if MMSE score falls below 10 and/or adverse events were recorded. A total number of 226 patients completed the study at month 21 (see Fig. 1 for details).

### 2.2. Statistical analysis

We called naive the group of first-time ACHEI-drug users, whereas non-naives were called the patients who have been taking this type of drugs even previously. *t*-Tests were performed to compare socio-demographic and clinical variables at baseline between the groups (naives versus non-naives). Non-parametric approach was also adopted to support results, performing Mann–Whitney test for each variable considered. Repeated-measure ANOVA was used to assess the efficacy of treatment, considering evaluation time as a within-subject factor and group as a between-subject factor. Sphericity assumption was checked using Mauchly's test (Mauchly, 1940) and Huynh–Feldt's correction (Huynh and Feldt, 1976) was adopted, if necessary, for the degrees of freedom. Size effects are reported as partial eta-squared values ($\eta_p^2$).

Linear and logistic regression analyses were performed to estimate predictors of responsiveness. To differentiate responders from the non-responders, the mean difference score for MMSE was computed between baseline and follow-up (after 21 months). Then, the distribution of scores was calculated, and four classes of responders were identified: "very good responders" (above the 75th percentile of the distribution), "good responders" (between the 75th and the 50th percentile) "bad responders" and "very bad responders" if patients scored between the 50th and the 25th and below the 25th percentile, respectively.

## 3. Results

At baseline, 188 patients were naives whereas 239 patients were not. After 21 months, 84 naives and 142 non-naives were included in the sample (Fig. 1).

### 3.1. Demographic and clinical characteristics of the two groups

One-way ANOVAs were performed for each variable of demographic and clinical data collected at baseline assessment (Table 1). Two variables showed significant differences: (i) the age: mean age of naives 78.5 ± 6.6 years (±SD); mean age of non-naives 77.0 ± 7.4 years ($p = 0.03$); (ii) disease duration, of naives: 44.9 ± 23.0 months, of non-naives 52.9 ± 24.6 months ($p = 0.001$). Non-parametric analyses (Mann–Whitney test) showed the same results.

### 3.2. Cognitive and functional outcomes

Large amount of literature information has shown that the three ACHEI nowadays available do not differ in efficacy but only in safety (Cummings, 2003; Lanctot et al., 2003a; Kaduszkiewicz et al., 2005). For this reason, we did not distinguish the drug type and considered rivastigmine and donepezil together.

Repeated-measure ANOVA was performed considering the five times of clinical assessments (baseline, 3, 9, 15, and 21 months) as within-subject factors and the group-distinction (naive versus non-naive) as between-subject factors. Three separate analyses were performed for each variable: MMSE, IADL and ADL scores (Fig. 2).

#### 3.2.1. MMSE

All main effects (group: $F_{(1, 224)} = 6.89$, $p = 0.009$, $\eta_p^2 = 0.03$; and time: $F_{(3.492,\ 782.136)} = 64.7$, $p < 0.001$, $\eta_p^2 = 0.22$) and interaction (group × time: $F_{(3.417,\ 782.136)} = 8.36$, $p < 0.001$, $\eta_p^2 = 0.04$) reached significance. We further analyzed data performing two separate ANOVAs, including time as within-subject factor only.

For the naive patients, ANOVA showed a significant main effect of time ($F_{(3.630,\ 316.791)} = 16.46$, $p < 0.001$, $\eta_p^2 = 0.17$). Bonferroni post hoc analysis revealed that MMSE differed from baseline (mean MMSE score = 19.6) at month 3 (mean MMSE score = 21.1, $p < 0.001$) and at month 21 (mean MMSE score = 18.3, $p = 0.006$).

In the case of non-naives, we found a significant main effect of the time ($F_{(3.264,\ 460.160)} = 69.51$, $p < 0.001$, $\eta_p^2 = 0.33$). Bonferroni post hoc analysis revealed that MMSE differed from baseline (mean = 19.7) at month 9 (mean = 18.7, $p = 0.009$), 15 (mean = 17.4) and at month 21 (mean = 15.9, $p < 0.001$).