Cholinesterase inhibitors in Alzheimer's disease: efficacy in a non-selected population

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Summary

This paper presents preliminary results on the efficacy of acetyl-cholinesterase inhibitors (ChE-I) administered in a population of patients with mild-to-moderate Alzheimer's disease (AD), recruited in the context of an Italian Department of Health supported project (Progetto Cronos). The patients were followed up for a maximum of 21 months. Around 45% of the subjects responded well to the treatment (i.e., stable or improved Mini Mental State) at the end of the 9th month. Thereafter, a global cognitive and functional decline was reported, more marked in basic daily activities. No factors (age, sex, disease duration, family history for AD, cognitive impairment at baseline) emerged as predictors of outcome.

KEY WORDS: acetyl-cholinesterase inhibitors, Alzheimer's disease, follow up.

Introduction

The pharmacological approach to Alzheimer's disease (AD) has altered since the introduction of acetyl-cholinesterase inhibitors (ChE-I). The efficacy of these compounds has been well documented in controlled randomized trials (1-8). A significant effect on cognition in patients with AD of mild to moderate degree has been confirmed, at least for the first year of treatment. In fact, a significant improvement at ADAS-cog has been detected in 50% (>4 points) and in 20% (>7 points) of patients, respectively (3). Patients under treatment have been found to show a decline of 1.5 points on the Mini Mental State (MMS) (9) after one year, as opposed to a decline of 3.7 points in untreated subjects (7). Moreover, the subjects under treatment showed a lower probability (40%) of developing functional decline compared with untreated patients (4). ChE-I also seem to be effective in AD of moderate to severe degree (MMS ranging from 5 to 17) (10). Recent observations underline the effects of these drugs not only on cognition, but also on behavioural disturbances (11,12). Some authors, moreover, suggest that ChE-I, even though their initial cognitive and functional benefit wanes with disease progression, can alter the natural history of AD, as indicated by delayed admission to nursing homes (13). There are no apparent differences in efficacy, evaluated by cognitive and functional measures, among the various available compounds (3,13,14).
September 2000 saw the start of an Italian multicentric project, "Progetto Cronos", organized by the Department of Public Health. The project provides for the prescription of commercially available ChE-I (donepezil, rivastigmine, galantamine) to AD outpatients with mild to moderate disease severity. A total of 517 Alzhiemer Assessment Units (AAUs), i.e., centres qualified to diagnose AD and to prescribe the drugs free of charge, are involved in the project. The aim of the project is to establish the real need for ChE-I in Italy and to verify their efficacy in everyday practice, i.e., in settings and populations vastly different from those of controlled pharmacological trials. In this way, a large number of patients have been granted access to the treatment for a long period of time. In our view, the project represents an ideal opportunity to gather important information on ChE-I treatment in a non-selected population.
We report the results, after 21 months of activity, obtained by the AAU at the IRCCS C. Mondino Institute of Neurology in Pavia.

Materials and methods

From September 2000 to August 2002 we recruited 321 AD patients (males 109, females 212, mean age 73.82±5.97, range 51-82 years). The mean disease duration was 18.53±3.67 months, range 10-31). Family history for AD was present in 23 cases (7%). Seventy-three patients (22%) had already undergone treatment with ChE-I, while 248 (78%) had never had any pharmacological therapy. The main clinical characteristics of the sample are shown in Table I (see over).
The diagnosis of AD was made according to NINCDS-ADRDA (15) and DSM IV criteria (16); diagnostic procedures followed Italian guidelines for the diagnosis of dementia (17). All the patients underwent neuroradiological investigation (at least a CT scan).
The Cumulative Illness Rating Scale (CIRS) (18,19)

was administered to each patient in order to obtain an index of comorbidity.
According to the Cronos Project inclusion criteria, only patients with AD of mild to moderate degree (MMS ranging from 14 to 26) could be admitted to the protocol. As regards the drug prescribed, the physician could choose freely from among the commercially available compounds, i.e., donepezil (5 or 10 mg/day), rivastigmine (from 6 to 12 mg/bid) or galantamine (from 16 to 24 mg/bid). Follow-up visits, for the monitoring of pharmacological response and side effects (and thus for possible dose adjustment or change of drug in the event of severe side effects) were scheduled after 4 (1st month) and after 12 weeks (3rd month) of treatment. Thereafter, the patients had to return every six months for clinical checks, i.e., after 9, 15, 21 months and so on.
To evaluate the clinical response, MMS, Activities of Daily Living (ADL), and Instrumental Activities of Daily Living (IADL) (20,21) were administered at each visit. According to the protocol, therapy had to be discontinued in the event of an MMS score of less than 10.

Table I - Clinical characteristics of the entire population (321 patients).

Males	109
Females	212
Mean age (yrs)	73.82±5.97 (range 51-82)
Mean disease duration (mths)	18.53±3.67 (range 10-30)
Schooling (yrs)	7.24±4.81 (range 3-17)
Family history of AD	23 (7%)
Previous treatment with ChE-I	73 (22%)
Never treated	248 (78%)
MMS	19.08±3.55 (range 14-26)
ADL	5.21±0.85 (range 3-6)
IADL	4.62±1.32 (range 2-8)
CIRS	2.91±1.45

Abbreviations: MMS=Mini Mental State; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; CIRS=Cumulative Illness Rating Scale.

Sixty-nine patients (21%) of the 321 discontinued the treatment. The causes were the following: death, not related to the treatment: 5; major strokes: 2; severe and rapid worsening: 24; severe side effects: 10; poor compliance, lost cases: 26; transfer to other AAUs: 2.
In this report we consider only those patients who had never undergone any pharmacological therapy (248 cases); of these, at the end of August 2002, 117, 64 and 20 subjects had completed the 9th, 15th and 21st months of treatment, respectively. Only 5/117 patients presented behavioural disturbances and were administered antipsychotics. The main clinical characteristics of these three groups – these 201 patients constitute the population whose results were submitted to statistical analysis – are reported in Table II.

Statistical analysis

The analysis of the results was performed using analysis of variance (ANOVA) for repeated measures and multivariate analysis. The critical value for statistical significance was set at $p<0.05$ for all measures.

Results

The trend of cognitive performances was analyzed by

Table III - MMS, IADL, ADL mean scores at different control visits (117 cases).

	Baseline	3rd month	9th month
MMS	18.71±3.06	18.74±3.11	18.00±3.42
IADL	4.73±1.18	4.72±1.17	4.59±1.11
ADL	5.42±0.69	5.39±0.69*	5.07±0.91**

Abbreviations: MMS=Mini Mental State; IADL=Instrumental Activities of Daily Living; ADL=Activities of Daily Living.

**3rd vs 9th month F= 9.11, p<0.003; **Baseline vs 9th month F= 10.90, p<0.001 (ANOVA for repeated measures).*

Table II - Main clinical characteristics of the population whose results were submitted to statistical analysis.

N. of cases (mths of treatment)	117 (9)	64 (15)	20 (21)
Males	44	20	6
Females	73	44	14
Mean age (yrs) range	73.72±6.07 53-85	74.16±6.12 53-85	73.91±6.09 53-85
Mean disease duration (mths) range	16.92±2.93 12-25	17.67±2.93 11-25	17.94±2.96 12-25
Schooling (yrs) range	7.19±5.98 3-17	6.37±4.58 3-15	6.45±5.63 3-17
Family history of AD	6 (5%)	4 (6%)	1 (5%)
CIRS	2.96±1.76	3.01±1.82	2.95±1.77

Abbreviations: CIRS=Cumulative Illness Rating Scale.

means of Repeated Measures ANOVA. Tables III, IV and V report the mean MMS, ADL and IADL values in the three different groups at the various follow-up visits. In the patients completing 9 months of treatment (117 cases), MMS and IADL scores remained stable at the 9-month follow up, only ADL values showed a significant decrease ($p<0.001$) (Table III); 53/117 (45%) patients could be considered responders (stable or improved MMS). In the patients treated until the 15th month (64 cases) we observed a worsening of MMS after the 9th month, no change in the IADL scores, and a significant worsening of the ADL scores, both at the 9th (as reported in the previous group) and at the 15th month (Table IV). Only 22/64 (35%) subjects were stable or improved on MMS. In the 20 patients followed for 21 months, MMS scores remained stable until the 15th month and then decreased ($p<0.05$), while ADL presented a significant worsening at the 15th and at the 21st months (Table V).

Two independent multiple regression models were performed in order to test relationships between the response variables at the first and second controls and the covariates in a multivariate setting. Response variables at 21 months were not tested, as the patient number was too small to allow statistically significant results. Variables were defined as follows:

– dependent: ΔMMS9 and ΔMMS15 respectively expressed as arithmetic difference between baseline, 9th and 15th month evaluation;
– independent: age: continuous; sex: females=0, males=1; baseline MMS: continuous evidence of familial AD: absent=0, present=1; years of disease: continuous.

Assumptions of normality were assessed using the Kolmogorov-Smirnov test and Stem and Leaf Plot.

Co-linearity among covariates was ruled out by means of uni- or bivariate tests.

Results of regression analyses are indicated in Tables VI and VII (see over).

Both models failed to reveal a significant relationship between the response variables and the possible predictors (Table VI, VII). Only in the second model were we able to observe a trend towards an inverse correlation between ΔMMS15 and baseline MMS ($p<0.076$) (Table VII).

Discussion

This study reports the preliminary results of ChE-I treatment in a non-selected AD population that differs greatly from the highly-selected populations investigated in randomised clinical trials, irrespective of the type of drug employed, and using very simple measures of outcome. Our data confirm that ChE-I have a positive effect in the treatment of AD at least for one year. Indeed, the therapy was found to slow down the progression of the cognitive and functional impairment in about 50% of the patients. This has to be considered a positive result, as we know from the literature that MMS decreases by about 2-3 points in a year in untreated AD. The efficacy appeared to decrease after one year and at the 15th month the percentage of subjects responding to treatment was down to 30%. We also evaluated the efficacy after 21 months of therapy. In this group the progres-

Table IV - MMS, IADL, ADL mean scores at different control visits (64 cases).

	Baseline	3rd month	9th month	15th month
MMS	18.73±3.40	18.75±3.43	18.03±3.44*	16.79±3.59**
IADL	4.49±1.40	4.52±1.37	4.49±1.30	4.18±1.22
ADL	5.59±0.56	5.54±0.56	5.23±0.84^{+}	4.70±0.88**

Abbreviations: MMS=Mini Mental State; IADL=Instrumental Activities of Daily Living; ADL=Activities of Daily Living.

*MMS *9th vs 15th month F=3.79, p<0.05; **Baseline vs 15th month F=9.39, p<0.003; **3rd vs 15th month F=9.51, p<0.003*
*ADL $^{+}$Baseline vs 9th month F=7.33, p<0.008; **Baseline vs 15th month F=44.51, p<0.0001; $^{+}$3rd vs 9th month F=5.75 p<0.001; **3rd vs 15th month F=39.56, p<0.00001; $^{+}$9th vs 15th month F=11.58, p<0.001 (ANOVA for repeated measures).*

Table V - MMS, IADL, ADL mean scores at different control visits (20 cases).

	Baseline	3rd month	9th month	15th month	21st month
MMS	19.35±3.50	19.40±3.62	19.20±3.51	18.16±3.60	17.09±3.43*
IADL	4.80±1.94	4.85±1.93	4.75±1.77	4.40±1.60	4.15±1.60
ADL	5.80±0.41	5.80±0.41	5.50±0.61^{+}	4.90±0.79**	4.65±0.88***

Abbreviations: MMS=Mini Mental State; IADL=Instrumental Activities of Daily Living; ADL=Activities of Daily Living.

*MMS *Baseline vs 21st month F=4.25, p<0.05*
*ADL **Baseline vs 15th month F=20.45, p<0.00001; ***Baseline vs 21st month F=30.56, p<0.0001; $^{+}$9th vs 15th month F=7.23, p<0.001 (ANOVA for repeated measures).*

sion of the disease seemed to be slower, but the number of subjects was too small to allow more definite conclusions to be drawn.

These data are in agreement with the literature (1-7), even though controlled clinical trials give higher percentages of responders. This can be explained by the fact that the populations of clinical studies are highly selected. The good results obtained in our non-selected population provide further confirmation of the efficacy of ChE-I.

Analysis of the results did not identify clinical predictors of therapeutic response, only a non significant trend between higher baseline cognitive performance and faster disease progression. This finding cannot be easily explained, and may merely reflect a statistical bias. It is important, however, to underline the good effect of ChE-I recently obtained in more severely impaired patients, too, a result that increases the possible applications of these compounds. Further, and in particular longer, observations are needed, together with advances in understanding of the pathogenetic mechanisms of AD (22).

Table VI - Multiple regression analysis at 9th month.

Covariates	Standardized coefficients	t	Sig.	β 95% confidence intervals	
	β			Lower limits	Upper limits
(Constant)		-.275	.783	-6.252	4.726
Sex	.123	1.297	.197	-.253	1.213
Age	-.029	-.302	.763	-.069	.050
Disease duration (years)	.123	1.257	.212	-.033	.146
Positive family history	-.018	-.193	.848	-1.294	1.064
Baseline MMS	-.044	-.454	.651	-.147	.092

Dependent variable: ΔMMS9.

Table VII - Multiple regression analysis at 15th month.

Covariates	Standardized coefficients	t	Sig.	β 95% confidence intervals	
	β			Lower limits	Upper limits
Sex		1.193	.238	-3.855	15.243
Age	-.012	-.098	.922	-1.384	1.254
Disease duration (years)	-.109	-.827	.412	-.150	.062
Positive family history	-.047	-.346	.731	-.286	.202
Baseline MMS	-.199	-1.580	.119	-3.096	.364
Sex	-.234	-1.803	.076	-.373	.019

Dependent variable: ΔMMS15.

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