Various outcomes of cholinesterase inhibitor treatment influence survival of patients with Alzheimer's disease.

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VARIOUS OUTCOMES OF CHOLINESTERASE INHIBITOR TREATMENT INFLUENCE SURVIVAL OF PATIENTS WITH ALZHEIMER'S DISEASE

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Conclusions

This longitudinal Alzheimer's disease (AD) study in routine clinical practice showed that longer survival could be expected for patients who receive and tolerate higher cholinesterase inhibitor (ChEI) doses and a longer duration of treatment.

Objectives

A varying response to and long-term outcomes of ChEI treatment have been reported among patients with AD. Whether the duration of treatment, type of ChEI agent, or dose affects mortality is unclear because few previous studies have investigated these relationships. An increased knowledge of the potential effect of ChEIs on patient survival is essential for both clinicians and the health services. We aimed to investigate the association between various aspects of ChEI therapy and lifespan in AD.

Methods

The Swedish Alzheimer Treatment Study (SATS) is a prospective, observational, multicentre study to evaluate the long-term treatment with ChEIs in a routine clinical setting. This study included 1,021 outpatients with a clinical diagnosis of mild-to-moderate AD (Mini-Mental State Examination score, 10–26) at the start of ChEI treatment (approximately the time of AD diagnosis). The cognitive and functional capacities of participants were evaluated semi-annually over 3 years. The patients' socio-demographic characteristics, ChEI dose, and date of death were recorded. The choice of drug agent and all decisions regarding dosage for each individual AD patient were left entirely to the discretion and professional judgment of dementia specialists.

Kaplan–Meier graphs were used to illustrate the differences in time to death (Figures 2–4). The distribution of time was compared using a log–rank test. One-way analysis of variance (ANOVA) with Bonferroni correction (Figures 2 and 4) and an independent-sample *t* test (Figure 3) were used to compare differences between the means.

Table 1. Baseline characteristics (*n* = 1,021)

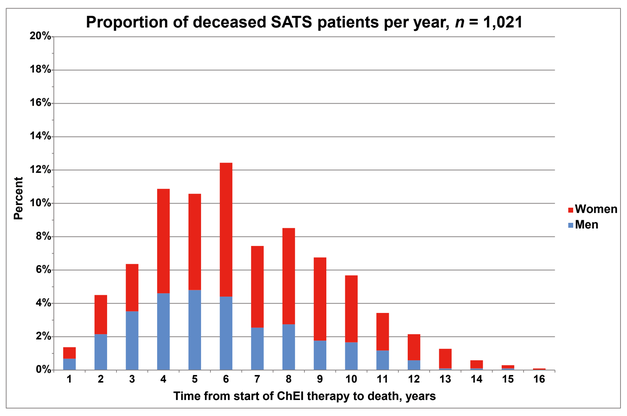
Female sex	654 (64%)
APOE ε4 carrier, (*n* = 999)	679 (68%)
3-year completion rate	376 (37%)
Estimated age at onset, years[a]	72.2 ± 7.3
Estimated duration of AD before diagnosis, years[a]	3.0 ± 2.1
Age at the start of ChEI treatment (baseline), years[a]	75.2 ± 7.0
Education, years[a]	9.4 ± 2.5
MMSE score, range 0–30[a]	21.4 ± 3.7
ADAS-cog score, range 0–70[a]	20.8 ± 8.9
IADL score, range 8–31[a]	15.9 ± 5.5
PSMS score, range 6–30[a]	7.5 ± 2.3
Number of concomitant medications[a]	2.9 ± 2.4
Length in the SATS, months[a]	23.2 ± 13.0
Time from AD diagnosis to death, years (*n* = 841)[a]	6.0 ± 2.9
Age at death, years (*n* = 841)[a]	82.0 ± 6.6

[a]mean ± standard deviation (SD)

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; APOE, Apolipoprotein E; ChEI, Cholinesterase inhibitor; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; PSMS, Physical Self-Maintenance Scale; SATS, Swedish Alzheimer Treatment Study.

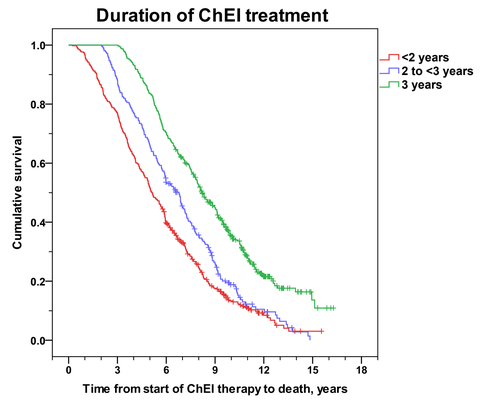
Results

Figure 1.



Proportion of deceased men and women per year after the initiation of ChEI treatment (shortly after AD diagnosis). After up to 16 years of follow-up, 841 (82%) of the participants in the SATS had died: 316 (86%) of the men and 525 (80%) of the women, *P*=0.021. The percentages of deceased patients were 12% after 3 years, 34% after 5 years, 54% after 7 years, and 75% after 10 years. Year 1 indicates a lifespan after baseline of up to 1 year, year 2 indicates >1 to ≤2 years, year 3 indicates >2 to ≤3 years, etc.

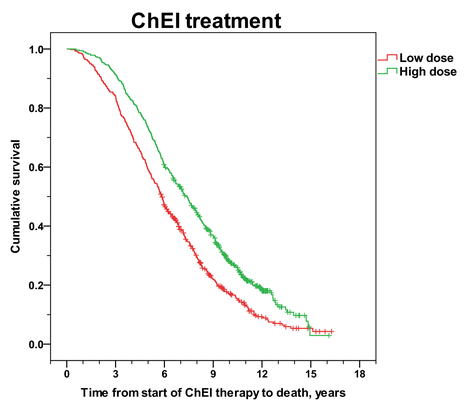
Figure 2.



Kaplan–Meier graph of the distribution of time from the initiation of ChEI therapy to death for three different groups based on length of time in the study. A log–rank test found significant differences for all pairwise comparisons (*P*<0.002).

For the 841 deceased patients, the mean (95% confidence interval (CI)) time from the start of treatment to death was 6.0 (5.8–6.2) years, and differed between individuals with varying durations of ChEI therapy in the study: 3-year completers (*n* = 279), 7.2 (6.9–7.5) years; 2 to <3 years (*n* = 183), 6.3 (5.8–6.7) years; and <2 years (*n* = 379), 4.9 (4.6–5.2) years, (*P*<0.001). No significant difference in lifespan was detected between the 1 to <2 years and the <1 year duration of ChEI groups.

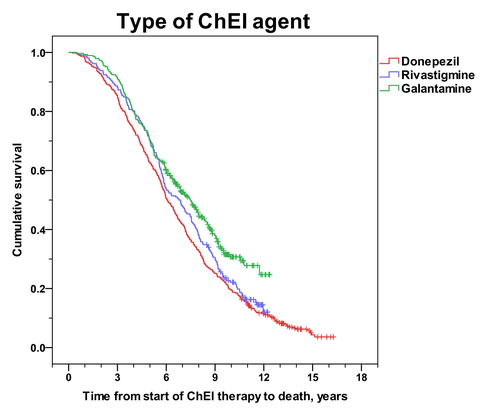
Figure 3.



Kaplan–Meier graph of the distribution of time from the start of ChEI treatment to death. A log–rank test showed a significant difference between high vs. low ChEI doses during the study, *P*<0.001. The median cut-off values were: donepezil 6.9 mg (*n* = 518), rivastigmine 6.0 mg (*n* = 212), and galantamine 15.0 mg (*n* = 291).

The deceased patients who received a higher mean dose of ChEIs during the study had a longer mean survival time than those who received a lower dose, 6.4 years (95% CI, 6.2–6.7 years) vs. 5.5 (5.2–5.8) years, *P*<0.001.

Figure 4.



Kaplan–Meier graph of the distribution of time from the start of ChEI treatment to death. A log–rank test showed a significant difference among the three ChEI drug agents; those who received galantamine had lower mortality compared with those who received donepezil and rivastigmine, *P*<0.032. However, the individuals in the galantamine group were younger and had better cognitive and functional abilities at baseline. No difference in survival between the types of ChEIs was found after adjusting for sex, age, and disease severity.

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