Author's response to reviews

Title: Response to cholinesterase inhibitors affects lifespan in Alzheimer's disease

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Author's response to reviews: see over
Response to the reviewers’ comments:

The authors thank professors Giacobini and Gu for their many valuable comments and opinions, which have helped to improve the manuscript.

Reviewer #1: Ezio Giacobini

Comments to the Author

1. TITLE OK but, why not,….. inhibitors affect…..

Response

We have changed the title according to the reviewer’s suggestion.

(1) The title was changed as follows.
“Response to cholinesterase inhibitors affects lifespan in Alzheimer’s disease”

Comments to the Author

ABSTRACT

2. Heterogeneous, differential response, please specify

Response

The text of the Background paragraph of the Abstract has been clarified. Please also refer to our response to comment #5.

(1) Abstract, background: the underlined text was changed as follows.
“A varying response to cholinesterase inhibitor (ChEI) treatment has been reported among patients with Alzheimer’s disease (AD). Whether the individual-specific response, specific ChEI agent or dose affects mortality is unclear.”

Comments to the Author

3. Conclusion: was tolerance the only criterium for dosage?

Response

The SATS patients received ChEI therapy according to the approved product labelling, as in routine clinical practice. The choice of drug agent (donepezil, rivastigmine, or galantamine)
and all decisions regarding dosage in this observational long-term study were left entirely to the discretion and professional judgement of individual clinicians (specialists in dementia disorders). Most patients received an increased dose after 4–8 weeks of treatment, and we aimed at further dose increases depending on the chosen ChEI agent. However, for some individuals, the dose was reduced because of side effects. Please also refer to our response to your comment #10.

(1) Abstract, conclusions: the underlined text was amended as follows.
“In individuals who received and tolerated higher ChEI doses, a longer lifespan can be expected.”

(2) Page 19, paragraph 2, line 1: the underlined text was amended as follows.
“In the present study, the patients who received and tolerated a higher dose of ChEI, …”

Comments to the Author

INTRODUCTION
4. Problem of mortality in AD, highly depending on comorbidity, difficult to point out a direct relationship with the disease, AD patients live longer and longer with better care, not rare are 15—20 yrs after diagnosis, the same in Parkinson.

Response

We have incorporated the reviewer’s relevant comments in the Introduction section.

(1) Page 4, paragraph 1, line 6: the underlined text was amended as follows.
“The mean lifespan after the time of AD diagnosis varies between 3 and 10 years, depending on the patient’s age; however, individuals with AD can live considerably longer, up to 15–20 years [3-5].”

(2) Page 5, paragraph 2, line 4: this text was amended as follows.
“Because co-morbidity often accompanies AD, it might be difficult to point out a direct relationship between the disease and survival time.”

Comments to the Author

5. Level of response is heterogeneous, please specify

Response

The text in the Introduction section has been clarified.

(1) Page 4, paragraph 2, line 9: the underlined text was amended as follows.
“However, not every patient with AD benefits from ChEI treatment, because the level of response varies among individuals.”
Comments to the Author

METHODS
6. Conflicting results about treatment-mortality relation: discuss in Discussion

Response

The Discussion has been expanded according to the reviewer’s suggestion.

(1) Page 15, paragraph 2, line 6: this text was amended as follows.
“Rountree et al. found that anti-dementia drug exposure was not significantly related to mortality in a community-based AD cohort that was followed for a mean period of 3 years. In a large-sample study of nursing-home residents with dementia, Gasper et al. observed that the survival rate after 2 years was higher in the ChEI-treated group compared with the untreated group. Nevertheless, individuals who are treated with ChEIs attend regular visits to their physician, and could also be receiving more aggressive pharmacological therapies against other co-morbid disorders, which might increase their length of life (ref. Gasper et al.). Both of the studies mentioned above included adjustment for a broad range of covariates, such as socio-demographic characteristics, dementia severity and major co-morbid illnesses. The patients with AD in the community-based cohort were 10 years younger, on average, than the nursing-home residents (73 vs 83 years). A recent study from our group that compared the SATS participants with untreated AD cohorts found no difference between these groups in patients aged < 85 years; however, a longer lifespan was observed among the ChEI-treated oldest old participants (ref. Wattmo et al.). Older individuals may have less hereditary and aggressive forms of AD. In addition, their cognitive reserve capacity may be reduced, which could lead to the detection of the disease, diagnosis and ChEI therapy at an earlier stage. In another study from the SATS, older age was reported as an independent predictor of better cognitive short-term response to ChEI and longitudinal outcome (ref. Wattmo et al.). These factors might imply a lower mortality rate in the oldest AD patients.”

(2) A new reference was added, as follows.
Wattmo et al. Dementia and Geriatric Cognitive Disorders 2014;38:286–299

Comments to the Author

7. Was the clinical diagnosis confirmed with autopsy? very important point related to comorbidity

Response

The clinical diagnosis of AD was not confirmed via autopsy, primarily because of a lack of neuropathological resources. This was a limitation of the study and has been noted in the Discussion section.

(1) Page 20, paragraph 1, line 3: this text was amended as follows.
“Another shortcoming of the study was that the clinical diagnosis of AD was not confirmed via autopsy.”
**Comments to the Author**

8. **Reason for using only the first 6 mo while treatment continued up to 3 years, treatment duration could be more relevant than treatment dosage.**

**Response**

The purpose of this study was to investigate differences in short-term response to ChEI therapy among AD patients, and their potential association with lifespan. A detailed description and analyses of mortality on duration of treatment and other important aspects of the long-term effects of ChEI, as well as the possible influence of cognitive and functional rates of disease progression on survival time, would represent a complex and lengthy study. Thus, a separate manuscript is planned that focuses on these essential issues, because we believe that those results deserve additional analyses, comparisons and discussions.

**Comments to the Author**

9. **Why to use only MMSE while ADAS-Cog data were available, both measures would have been better to evaluate relation to treatment effect.**

**Response**

Both MMSE and ADAS-cog scores were investigated throughout the manuscript, as stated in the Methods section, page 9, paragraph 3, line 4; and the results were presented in Table 2 in the original manuscript. In contrast with MMSE score, the change in ADAS-cog score during the first 6 months of ChEI treatment did not influence lifespan. These results were clarified in the text. These changes have been introduced in the manuscript.

(1) Abstract, Results: the underlined text was amended as follows.

“A longer lifespan (mean of 0.5 years) was observed among the improved/unchanged patients, as measured by MMSE or CIBIC score, but not by ADAS-cog score, after 6 months of ChEI therapy.”

(2) Page 12, paragraph 2, line 5: the underlined text was amended as follows.

“A longer time to death was associated with a more positive response in cognitive (MMSE model, but not ADAS-cog model) or functional ability …”

(3) Page 16, paragraph 2, line 5: this text was amended as follows.

“No difference in mortality among the responder groups was observed when using the ADAS-cog scale. The ADAS-cog is a more complex cognitive measure than the MMSE test, and it includes a greater number of items. The proportion of patients who were categorized as improved/unchanged according to ADAS-cog was smaller compared with that categorized using the MMSE scale, which might be one explanation for this inconsistent result.”

(4) Page 21, paragraph 1, line 3: the underlined text was amended as follows.
“In conclusion, the present study of response to ChEI after 6 months of treatment showed a few months prolonged lifespan among the improved/unchanged patients regarding cognition (MMSE score, but not ADAS-cog score), …”

Comments to the Author

10. Were all 14 sites standardized to diagnosis and treatment?

Response

Specialists in dementia disorders diagnosed the patients in all centres (memory clinics) included in the SATS. Only 1–2 dementia specialists were working in most of the centres; thus, the same clinician often followed the individual patient during the entire study. The responsible specialists and other staff at all participating SATS centres received joint, uniform training in Good Clinical Practice, in diagnostics, in usage of the rating scales and regarding the performance of the assessments and the study. These changes have been introduced into the manuscript.

(1) Page 6, paragraph 2, line 5: this text was amended as follows.
“The SATS participants were diagnosed by specialists in dementia disorders.”

(2) Page 7, paragraph 2, line 6: the underlined text was amended as follows.
“After inclusion and baseline assessments, the participants were prescribed ChEIs according to the approved product recommendations, as in routine clinical practice. 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. Most patients received an increased dose after 4–8 weeks of treatment, and we aimed at further dose increases depending on the chosen ChEI agent. However, for some individuals, the dose was reduced because of side effects. The responsible specialists and other staff at all participating SATS centres received joint, uniform training in Good Clinical Practice, in diagnostics, in usage of the rating scales and regarding the performance of the evaluations and the study. In addition, research nurses from the main centre (Memory Clinic, Malmö) supervised the SATS via careful monitoring and personal visits to the various centres throughout the entire study.”

Comments to the Author

11. 63 % patients showed stabilization/no-change or improvement: how many were stable and how many were improved? again ADAS-Cog is important.

Response

These results were added to the original manuscript.

(1) Page 12, paragraph 3, line 2: the underlined text was amended as follows.
“Among them, 161 individuals (24%) exhibited improvement, i.e., had an increase of 3 or more MMSE points. The improved/unchanged MMSE group exhibited a longer lifespan after the baseline than did the deteriorated group (6.03 ± 2.78 vs 5.48 ± 2.64
years; $t(671) = 2.52; P = 0.012$). No significant difference was detected between the improved and unchanged AD patients.

“Regarding the ADAS-cog score, 333 patients (49%) showed improvement/no change (<0 point change) after 6 months of ChEI therapy. Among them, 167 individuals (25%) exhibited improvement, i.e., had a decrease of at least 4 ADAS-cog points. The 6-month change in ADAS-cog score showed no significant association with survival time.”

Comments to the Author

DISCUSSION

12. Milder disease severity shows more favourable response: some studies showed the opposite with best results in more severe patients. Discuss,

Response

The discussion was expanded according to the reviewer’s suggestion.

(1) Page 17, paragraph 1, line 3: this text was changed as follows.

Removed text:

“A paper from our SATS reported that individuals who initially exhibited a more positive functional response to ChEI therapy were less cognitively impaired at the baseline and showed a significantly higher ADL capacity after 3 years of treatment [35]. Therefore, the participants’ cognitive and functional scores were included in our general linear models as independent predictors. Nevertheless, the responders exhibited a significantly longer survival. The abovementioned findings indicate that response to ChEI, as measured using different scales, prolongs life by a few months in AD.”

Revised text:

“However, a subsequent faster deterioration over time was observed in the patients who were more severely impaired after their initial response to therapy (ref. Wattmo et al). A greater reversible cholinergic deficit in the more advanced stages of AD is a possible explanation for the finding mentioned above, suggesting that this subpopulation is more responsive to ChEI (ref. Davis et al.). Another explanation might be that the change in the score on a certain assessment scale is expected to be larger at the level of function, e.g., moderate AD, at which the scale measures the person’s abilities most accurately (ref. Liu et al.). Articles stemming from the SATS reported that a higher cognitive status at the baseline was associated with better longitudinal outcome in cognition (ref. Wattmo et al.), and that individuals who initially exhibited a more positive functional response to ChEI therapy were less cognitively impaired at the baseline and showed a significantly higher ADL capacity after 3 years of treatment [35]. Therefore, the participants’ cognitive and functional scores were included in our general linear models as independent predictors. Nevertheless, the responders exhibited a significantly longer survival. The above-mentioned findings indicate that response to ChEI, as measured using different scales, prolongs life by a few months in AD patients. A more preserved cognitive status at the start of therapy can lead to a better ability to maintain higher levels of cognitive and ADL performance over longer periods, which underscores the importance of initiation of anti-dementia drugs at an early stage of the disease.”

(2) New references were added, as follows.
Comments to the Author

13. Possible relation to treatment duration. Discuss

Response

Please refer to our response to comment #8.

Comments to the Author

14. Comorbidity and autopsy results: Discuss

Response

As mentioned in comment #7, the clinical diagnosis of AD was not confirmed by autopsy in the SATS. The discussion regarding co-morbidity has been expanded; please see below.

(1) Page 18, paragraph 1, line 4: this text was amended as follows.

“Because concomitant illnesses are commonly observed in elderly persons, it is difficult to investigate direct associations between AD and lifespan. In the present study, we adjusted the multivariate models for usage of different types of medications. Nevertheless, other factors related to co-morbidity might affect survival time in AD, such as severity and type of somatic disorders or psychiatric symptoms, which were not addressed by the variables included in the models.”

Comments to the Author

15. Other factors to be considered.

Anti-inflammatory effect of ChEI

Immunological factors

Quality of life and caregiver burden to be considered

Response

Immunological factors, quality of life and caregiver burden were not investigated in the SATS. The importance of measuring quality of life and caregiver burden in future studies was mentioned in the Discussion, page 17, paragraph 2, line 4 in the original manuscript. These changes have been introduced into the manuscript.

(1) Page 20, paragraph 1, line 4: this text was amended as follows.

“Additional factors that were not investigated in the SATS might also influence mortality. For example, a recent study reported by our group found that cerebral inflammation independently predicted an early death in AD. The effect of ChEI was not addressed in that study (ref. Nägga et al.). Furthermore, ChEI therapy could
entail wide-spread effects beyond the central nervous system that might affect lifespan. ACh synthesis has been detected in various types of immune cells, muscle cells and epithelial cells (e.g., of the airways and of the alimentary and urogenital tracts) (ref. Wessler et al.). A review of the role of ChEIs in the modulation of the immune response reported that these drug agents might influence the immune system (ref. Pohanka).

(2) Page 20, paragraph 2, line 3: the underlined text was amended as follows.
“Regardless of whether response to ChEIs prolongs life, other aspects that were not evaluated in the SATS, such as the patients’ quality of life and the caregiver burden during this extended time, need to be investigated.”

(3) New references were added, as follows.
Nägga et al. Alzheimer’s Research & Therapy 2014;6:41
Wessler et al. Life Sciences 2003;72:2055–2061

Reviewer #2: Yian Gu

Comments to the Author

1. Major Compulsory Revisions:
1.1 The author may want to make a clearer statement of the study goal. It is unclear whether the study aims to examine the association between response to ChEI, or the dosage of ChEi, and the life-span. It seems both have been examined. But the tables (2 and 3) seems to just focus on the ‘response to ChEI’, and the discussion have too many of the other covariates (education, male, etc.). All these make the study goal very confusing.

Response

The relation between lifespan and response to ChEI treatment in AD is complex. Many parameters, such as genetic, socio-demographic, disease-related and co-morbidity factors affect both survival time and the individual’s response to ChEI. For example, male sex, older age, presence of the APOE ε4 allele and more cognitive impairment are commonly related to a shorter length of life. In addition, male sex, older age, APOE ε4 non-carrier status and more cognitive impairment have been associated with better cognitive short-term response to ChEI therapy in some studies. Therefore, we consider that it is necessary to discuss these covariates, to increase the understanding of the relationships among lifespan, response to ChEI and these variables. The aims of the study have been clarified.

(1) Page 5, paragraph 4, line 1: the underlined text was amended as follows.
“The aims of this study were 1) to examine the relationship between lifespan and the short-term response to ChEI treatment, 2) to investigate associations among survival time, drug agent and dosage of ChEI, and 3) to identify potential predictors that might influence these outcomes.”

Comments to the Author
2. Minor Essential Revisions
2.1 The paper needs a clear hypothesis.

Response

Our hypothesis was that groups of AD patients with varying levels of short-term response to ChEI treatment also exhibit differences in lifespan after diagnosis. Please, also refer to the clarifications in the aims of the manuscript, comment #1.

Comments to the Author

2.2 The authors mentioned in the last sentence of the first paragraph of page 15 ‘...with no increase in survival in the severe disease stage.’ However, no data of ‘severe disease stage’ were available in this study, so such a statement is not supported by the findings of the study.

Response

We have clarified this expression.

(1) Page 17, paragraph 1, line 20: this text was changed as follows.

Removed text:
“The observed posttreatment delays in symptom progression suggest that the patients’ increased length of life occurs at a higher cognitive and functional level, with no increase in survival in the severe disease stage.”

Revised text:
“The effects of initial response to ChEI and the subsequent post-treatment delays in symptom progression suggest that the observed mean 6-month increase in lifespan occurs at a higher cognitive and functional level and not in the later, more advanced stages of AD.”

Comments to the Author

2.3 The study did not examine whether 'specific agent' was associated with lifespan, while it was mentioned in the 'introduction' of the abstract. It would be interesting to see whether the three types of ChEI have different relationship with lifespan of the patients.

Response

Whether specific ChEI agents were associated with lifespan was investigated in the study. This was mentioned in the Methods section, page 9, paragraph 3, last line in the original manuscript. This result has been clarified in the text.

(1) Page 14, paragraph 1, line 4: the underlined text was amended as follows.

“No significantly different effect on lifespan was found among the three drug agents after adjusting for age at the baseline and the interaction effect of type of ChEI with age.”
2.4 The outcome measure should be the lifespan, rather than the response to ChEI measures.

Response

The outcome measure (dependent variable) used in the general linear models was lifespan. This was stated in the Methods section, page 9, paragraph 3, line 5, and was described in Tables 2 and 3 in the original manuscript.

2.5 On page 16, the last sentence of the first paragraph, ‘A higher education could be a risk factor in AD...’. Right before this sentence, the authors mentioned ‘... a higher education level...... later detection of the disease.’ Higher education, as a major cognitive reserve factor, should not be considered as a risk factor for developing AD. The author probably wanted to mean ‘a higher education level was associated with worse prognosis in AD?’

Response

The reviewer is correct. The wording has been rephrased.

(1) Page 19, paragraph 1, line 3: the underlined text was amended as follows. “A higher level of education can be a risk factor for worse prognosis in AD, ...”

Discretionary Revisions

3.1 In the last paragraph on page 16: The study found ‘higher dose ....exhibited... extension in life-span’. This finding does not support ‘the importance of optimizing the ChEI dose for each individual with AD’. This would just lead to a suggestion of ‘higher dose would be beneficial as long as the patients can tolerate’.

Response

The sentence was changed according to the reviewer’s suggestion.

(1) Page 19, paragraph 2, line 6: this text was changed as follows. “These results show that a higher ChEI dose would be beneficial as long as the individuals can tolerate this medication.”

Yours sincerely,

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