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Initial cognitive response to cholinesterase inhibitors and subsequent long-term course in patients with mild Alzheimer disease

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Abstract

Background: Some guidelines recommend to discontinue treatment with cholinesterase inhibitors (ChEIs) in patients with Alzheimer's disease (AD) without an initial response to ChEI treatment. Evidence supporting this recommendation, however, is limited. This study aimed to investigate the relation between the initial cognitive response to ChEI treatment and the subsequent long-term course of cognition of AD patients.

Methods: The Frisian Alzheimer's Disease Cohort study is a retrospective longitudinal study of 576 community-dwelling AD patients treated with ChEIs in a 'real-life' setting at a large memory clinic. A repeated measures analysis using a marginal model (population based averaged model) was applied to investigate whether there is a difference in the subsequent long-term course of cognition (Mini Mental State Examination (MMSE)) between initial non-responders and responders. Absence of an initial response was defined as a lower MMSE score after the first 6 months of treatment compared to baseline, a positive response as the same or a higher MMSE score.

Results: At baseline, median age was 80 years and the median MMSE score 23. Non-responders showed a slower rate of cognitive decline in the three subsequent years than responders, with a mean annual MMSE decline of 0.9 points versus 1.2 points, respectively ($p<0.0001$).

Conclusion: Our results suggest that it is not appropriate to discontinue ChEI treatment solely based on the absence of an initial cognitive response.

***Key words**:* Alzheimer disease, 'real-life' setting, cholinesterase inhibitors, treatment response, course of cognition, longitudinal study

Introduction

It is estimated that by 2030 about 65 million people will be affected by dementia worldwide (Prince *et al.,* 2013). Alzheimer's Disease (AD) is the most frequent cause of dementia (Ferri *et al.,* 2005; Reitz *et al.,* 2011) and characterized by cognitive impairment, functional decline and neuropsychiatric symptoms (Burns and Iliffe, 2009). As a consequence, AD has substantial effects on the quality of life of patients and their caregivers (Schölzel-Dorenbos *et al.,* 2009).

Unfortunately, there is no cure for AD. The cholinesterase inhibitors (ChEIs) galantamine, rivastigmine, and donepezil are recommended for the symptomatic management of mild to moderate AD (National Institute for Health and Clinical Excellence, 2006; National Institute for Health and Clinical Excellence, 2011; Kwaliteitsinstituut voor de gezondheidszorg CBO, 2005). Some guidelines on the management of AD propose to evaluate the effect of ChEI treatment three or six months after the ChEI is started (Kwaliteitsinstituut voor de gezondheidszorg CBO, 2005; Ministry of Health Singapore, 2007; Quaseem *et al.,* 2008). In case of deterioration of global, cognitive, functional or behavioral function during the first months of treatment, the patient is considered to be a non-responder and discontinuation of treatment is recommended (Kwaliteitsinstituut voor de gezondheidszorg CBO, 2005; Ministry of Health Singapore, 2007; Rabins et al., 2007). However, the evidence demonstrating that it is appropriate to stop treatment in non-responders is limited (Quaseem *et al.,* 2008). In contrast, it has been shown that beneficial effect of ChEIs disappear within six weeks after discontinuation (Gaudig *et al.,* 2011). Some guidelines make no statements about the evaluation of treatment effect (Hort et al., 2010; Scottish Intercollegiate Guidelines Network, 2006). The National Institute for Health and Clinical Excellence recommends that treatment should be continued only when it is considered to have a worthwhile effect (National Institute for Health and Clinical Excellence, 2006; National Institute for Health and Clinical Excellence, 2011).

Understanding the relation between the initial response to ChEI treatment and the subsequent course of AD is important given the potential negative consequences of stopping treatment. This study aimed to investigate the relation between the initial cognitive response to treatment with ChEIs and the subsequent long-term course of cognition of AD patients in a 'real-life' setting.

Methods

Study design

The Frisian Alzheimer's Disease Cohort study is a retrospective longitudinal study of AD patients treated with ChEIs in a 'real-life' setting. To evaluate the relation between the initial cognitive response to treatment with ChEIs and the subsequent course of cognition, we investigated whether there is a difference in the subsequent long-term course of cognition between non-responders and responders. Absence of an initial response was defined as a lower Mini Mental State Examination (MMSE) score after the first 6 months of treatment compared to baseline (i.e. the period in which the diagnosis AD was made and patients started with a ChEI), a positive response as the same or higher MMSE score compared to baseline. Because the evidence demonstrating that it is appropriate to stop treatment in non-responders is limited (Quaseem *et al.,* 2008) and the potential negative consequences of stopping treatment (Gaudig *et al.,* 2011), patients from our clinic continued treatment, even in the absence of a treatment response after the first six months of treatment.

Setting and participants

The study was conducted with data from 576 AD patients seen at a memory clinic of the Medical Center Leeuwarden, situated in the north of the Netherlands, during the period 2002 to 2012, though most patients were diagnosed with AD between 2006 and 2010 (87.3%). All patients were

diagnosed in accordance to the criteria of the National Institute of Neurological and Communicative Diseases – Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) (McKhann *et al.,* 1984). Additional inclusion criteria were, age 65 years or older, start with a ChEI and living at home or in residential care during the period the diagnosis AD was made. Since the definition of response is based on the change in MMSE score between baseline and the first 6-month assessment, patients had to have both a baseline and the first 6-month assessment. Various patient characteristics were recorded during the outpatient clinic visits. The first control visit (i.e. follow-up visit) was planned six months after the start of a ChEI and subsequent control visits were annually. The total number of visits per patient ranged from 1 to 11, the median number was 3 (25^{th} – 75^{th} percentile 2 - 5). When treatment with ChEIs was discontinuated, the outpatient visits ended. The initial assessments were carried out by physicians of the multidisciplinary team of the memory clinic. The control visits were carried out by experienced dementia nurses under supervision of geriatricians. Data were retrospectively collected and entered into the study database. The study was approved by the local ethics committee of the Medical Center Leeuwarden.

Measurements

Socio-demographic characteristics

Age, gender, social status, comorbidity, weight, use of informal care and number of types of professional care were recorded (i.e. five types of professional care were distinguished: dementia case management, household help, home nursing, respite care (i.e. daycare center) and meals at home services). Comorbidity was evaluated by the Cumulative Illness Rating Scale (CIRS). The total CIRS score ranges from 0 (no impairment) to 56 (extremely severe impairment) (Salvi *et al.,* 2008). AD as index disease was not included in the CIRS score. The number of medications beside the ChEI was recorded; polypharmacy was defined as total use of 4 or more medicines beside the ChEI.

Cognitive functioning

Cognitive functioning was assessed by the MMSE (Folstein *et al.,* 1975) and the clock-drawing test (Shulman *et al.,* 1993).

Behavioral and psychological symptoms (BPS) of dementia

Based on self reported patient and caregiver information, we recorded whether BPS were present or absent. Since BPS was not operationalized with a measurement instrument, it was not possible to report the severity, nature or frequency of BPS.

Type and dosage of ChEI

At each outpatient clinic visit, type and dosage of ChEI were recorded. If applicable, adding of memantine or switch to memantine was recorded. At our memory clinic, the extended release form of galantamine is the treatment of first choice for patients with mild to moderate AD. The extended release form of galantamine is prescribed since 2005 at our memory clinic. Before 2005, galantamine was given twice daily. Patients start with 8 milligram (mg) galantamine per day for at least four weeks, followed by a maximum dose of 16 mg/day for at least four weeks and, if necessary (for example in case of severe BPS) , then the dose was increased to the maintenance dose of 24 mg/day.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) 16.0 and Statistical Analysis Software (SAS) 9.2. All hypothese tests were two-tailed. A probability (p) value of less than 0.05 was considered statistically significant. Descriptive statistics are presented as means ± standard deviations for normally distributed variables. For skewed distributed variables, median and 25^{th} – 75^{th} percentiles are given. We used the Kolmogorov Smirnov test to establish the distribution of the variable. Number and proportion are given for categorical variables.

To investigate whether there is a difference in the subsequent course of cognition between non-responders and responders, we applied a repeated measures analysis using a marginal model (population based averaged model) and SAS proc mixed procedure with time as repeated statement and unstructured covariance structure. The repeated measures analysis has been developed for the analysis of longitudinal, continuous, dependent data. It gives an estimate of change in the dependent variable over time. In the present study, MMSE score was used as dependent variable, time (i.e. the number of measurement moments) and the response group (responder or non-responder after the first six months of treatment) were included as independent variables. The analyses were performed with all available data from patients with a baseline assessment and the first 6-month assessment, over a period of maximally 3.5 years (five measurements). From the 6^{th} measurement moment, it was not possible to give a reliable estimate of change in MMSE due to the small number of patients at that moment.

Various characteristics were compared between responders and non-responders, respectively between patients included in the repeated measures analysis and patients who could not be included in the repeated measures analysis and between patients immediately treated with a ChEI and patients not immediately treated with a ChEI. The independent sample t-test was performed to compare normally distributed variables. We employed the Mann-Whitney U test to compare skewed distributed variables. The Pearson chi-square or Fisher's exact test were used to compare categorical variables

Results

Patient characteristics

335 Patients were included. 241 Patients were excluded because they did not have a baseline assessment or the first 6-month assessment. At baseline, median age was 80 years (25^{th} – 75^{th} percentile 75.0 – 83.0) and median MMSE score 23 (25^{th} – 75^{th} percentile 20.0 – 25.0) (table 1). Almost half of the patients (45.8%) were independent of professional care, but the majority (81.9%) received informal care. Of the included patients, 97.6% started with galantamine and 2.4% with rivastigmine. No differences in baseline characteristics were found between patients included (n=335) and excluded (n=241) in the repeated measures analyses (table 2). In addition, no differences in baseline characteristics were found between patients immediately treated with a ChEI (n=519, 90.1%) versus patients not immediately treated with a ChEI (n=57, 9.9%). During follow-up, memantine was added in 81 (14.1%) patients of whom 38 were included in the repeated measures analysis (18 non-responders and 20 responders). 18 Patients (3.1%) switched to monotherapy with memantine of whom 12 were included in the repeated measures analysis (3 responders and 9 non-responders).

Course of cognition: non-responders versus responders

An initial response was absent in 155 patients (46.3%; non-responders) and present in 180 patients (53.7%; responders) (table 2). Baseline MMSE score was higher in non-responders than in responders due to the higher number of patients with very mild AD and the lower number of patients with moderate AD in non-responders compared to responders (table 2). During the three subsequent years (i.e. from measurement moment 2), the fitted MMSE score of non-responders was lower than of responders (figure 1a, table 4). The rate of cognitive decline, however, was slower in non-responders than in responders, with a mean annual MMSE decline of 0.9 points versus 1.2 points respectively ($p<0.0001$) (table 4, figure 1a). Non-responders used more medications and had more types of professional care at baseline (table 2). No differences were found in the dosage of galantamine between responders and non-responders during 42 months of follow up, nor in the use

of other medication (i.e. rivastigmine, galantamine in a dosage of 8 mg/day, memantine or a combination of memantine with rivastigmine or galantamine) (table 3).

Discussion

To our knowledge, this is one of the largest studies examining the relation between the initial cognitive response to ChEI treatment and the subsequent long-term course of cognition in AD patients. Our results show that non-responders had a slower rate of cognitive decline during the subsequent 3 years than responders. The rate of decline in MMSE score in non-responders is also slower compared to the rate of decline in historical cohorts with untreated patients. In these cohorts, the estimated annual rate of decline in MMSE score was 3.3 points (Han *et al.,* 2000) (figure 1b). This estimated rate of decline is based on a meta-analysis of 37 studies, involving 3492 untreated AD patients, and is applicable to the course of AD during the first 1 or 2 years after initial examination (Han *et al.,* 2000), like the patients from our cohort. Contrary to the recommendations in most current guidelines (Kwaliteitsinstituut voor de gezondheidszorg CBO, 2005; Ministry of Health Singapore, 2007; Rabins et al., 2007), our findings suggest that despite absence of an initial response to treatment with a ChEI, treatment can be beneficial in reducing the rate of decline during subsequent long-term course of cognition in AD patients.

As far as we know, no other studies investigated the relation of the initial cognitive response to the subsequent rate of cognitive decline in the way we did. Five Italian studies, all part of the Cronos project, investigated whether a cognitive response at three months predicted cognitive outcome (i.e. absolute MMSE score) at 9, 15 and 21 months (Caffarra *et al.,* 2007; Calabria *et al.,* 2009; Raschetti *et al.,* 2005; Rota *et al.,* 2007; Mossello *et al.,* 2004). They showed that patients with a response at three months had a better cognitive outcome at all three endpoints than patients without a response (Caffarra *et al.,* 2007; Calabria *et al.,* 2009; Raschetti *et al.,* 2005; Rota *et al.,* 2007; Mossello *et al.,*

2004). This confirms our result that the mean MMSE score of responders was higher than that of non-responders during the subsequent disease course. The authors of the Italian studies suggest that if cognitive improvement is not detectable during the first three months, treatment should be reconsidered (Raschetti *et al.,* 2005; Rota *et al.,* 2007; Mosello *et al.,* 2004). However, they looked at absolute MMSE scores (i.e. disease severity), not at the rate of decline (i.e. disease progression). Given the slower rate of cognitive decline in non-responders in our study, a treatment effect in non-responders can not be excluded and therefore, we think that it is not justified to reconsider treatment in case of absence of an initial response. It must be taken into consideration that comparison with our results is hampered by differences in patient characteristics (i.e. patients in the Italian studies were younger (mean age 72-78 years) and more cognitively impaired at baseline (mean baseline MMSE 18-19, i.e. moderate AD)). In addition, the length of follow-up was shorter in the Italian studies, ranging from 9 to 30 months (Caffarra *et al.,* 2007; Calabria *et al.,* 2009; Raschetti *et al.,* 2005; Rota *et al.,* 2007; Mossello *et al.,* 2004). Most importantly, the definition of treatment response differed between our study and the Italian studies, and between the five Italian studies; none of the Italian studies used the same definition.

In the present study, the baseline MMSE score of non-responders was higher than of responders. This is in accordance with results from studies identifying factors affecting ChEI treatment response (Caffarra *et al.,* 2007; Calabria *et al.,* 2009; Wallin *et al.,* 2009; Van der Putt *et al.,* 2006; Pakrasi *et al.,* 2003), showing that patients with a lower baseline MMSE score were more likely to respond. One explanation may be that the MMSE is not able to detect an increase in MMSE score in patients with high MMSE scores, i.e. a ceiling effect. Another explanation put forward has been that patients with lower MMSE scores have a larger cholinergic deficit (Perry *et al.,* 1978) and that the effect of increasing cholinergic levels with ChEIs in these patients is larger (Van der Putt *et al.,* 2006). This could also explain the slower rate of decline in MMSE score in non-responders, because the mean MMSE score of non-responders was lower compared to responders during the subsequent course.

Our result of a slower cognitive decline in non-responders might also be explained by the difference in disease stage between responders and non-responders, i.e. more patients in the non-response group had very mild AD and less patients had moderate AD compared to the response group. Since MMSE in AD is known to follow a curvilinear, downward-accelerating course (Mendiondo *et al.,* 2000), it is possible that the difference in rate of cognitive decline between responders and non-responders reflects a difference in rate of decline at different stages of AD. Moreover, the difference in rate of decline between responders and non-responders might be explained by a difference in the dose of galantamine between responders and non-responders, because the efficacy of ChEIs is dose dependent (Cummings *et al.,* 2012). Though, no differences were found in the dose of galantamine between responders and non-responders.

Some limitations of the present study must be considered when interpreting the findings. We did not have a control group that was not treated with a ChEI. Hence, we were restricted to evaluate the rate of decline in MMSE score in responders and non-responders with data derived from historical pre-ChEI-era AD cohorts. These comparisons have shortcomings, such as differences in methodology and clinical characteristics. Since this was a retrospective study, we were dependent on available data collected in the past. As a consequence, some data were not available, for instance information on activities of daily living measured with a valid scale. Hence, the change in MMSE score was the only measure available to determine treatment response. The MMSE has shortcomings such as an inability to detect change in severely demented patients (Han *et al.,* 2000). However, the MMSE performs well in mild to moderate AD patients (Han *et al.,* 2000). Our definition of response is based on an outcome measure most often used in clinical practice and as described in the Dutch guideline regarding the management of AD (Kwaliteitsinstituut voor de gezondheidszorg CBO, 2005). Though, it can not be assumed that this definition of treatment response correlates with what is considered a relevant outcome by patients and their caregivers. Moreover, this definition includes changes that lie within the margin of error for test-retest reliability on the MMSE (Hensel *et al.,* 2007). Unfortunately,

no consensus exists regarding the definition of treatment response. Development of scales that can describe the overall course of AD in terms of patient-relevant outcomes are needed. Recently, such a scale was developed: the Relevant Outcome Scale for Alzheimer's Disease (ROSA) (Holthoff *et al.,* 2011). The ROSA may possibly be helpful in defining a patient-relevant treatment response. Furthermore, patients without a baseline assessment or first 6-month assessment could not be included in the repeated measures analysis. The fact that there were no differences in baseline characteristics between patients who could be included, versus those who could not be included in the repeated measures analysis, makes the probability of selection bias unlikely. Though, the absence of differences in baseline characteristics between patients included and excluded in the analyses does not mean that their disease course over the first six months was similar. Therefore, the probability of selection bias can not fully be excluded. In addition, the decision to start the patient on a ChEI was made by the physicians of the memory clinic, which may also have contributed to selection bias.

A major strength of the present study is its 'real-life' setting, thereby avoiding the limitations of most AD clinical trials, such as the use of strict inclusion and exclusion criteria that could limit the external validity (Fortin *et al.,* 2006; Rothwell, 2005; Cummings, 2003). In addition, we used data from a properly defined cohort. Another strength is the use of the repeated measures analysis. Statistical analysis of longitudinal data is complicated because of interdependency of measurements and, particular in older AD patients, drop out of patients (Mohs *et al.,* 2000). A repeated measures analysis is specifically developed for the analysis of longitudinal dependent data. All data contribute to the longitudinal analysis and even data from patients who dropped out can be used. This way we could include a large number of patients with a long length of follow up. However, the applied repeated measures analysis using a marginal model also has limitations. Since for the marginal model Missing Completely At Random (MCAR) assumptions apply, missing data should be completely at random. We think that our data meets the MCAR assumption since the main reason for missing data

in our cohort is that patients were still waiting for their next outpatient clinical visit at that moment of data collection. However, due the nature of our population (i.e. elderly patients with AD), it can not be fully excluded that all the missing data in our study was completely at random. In addition, since time was treated as categorical variable, variability in visit scheduling was ignored, potentially limiting the statistical power of our study. However, due to our strict follow-up program, the variability in visit scheduling was very limited.

Conclusion

In this study, the long-term cognitive decline in patients without an initial cognitive response to ChEI treatment is slower compared to patients with a positive initial response. In addition, the rate of cognitive decline is slower compared to the rate of decline in historical pre-ChEI-era cohorts. Therefore, a beneficial effect of treatment in initial non-responders can not be excluded. These results suggest that discontinuing ChEI treatment solely based on the absence of an initial cognitive response might not be appropriate.

Conflict of interest declaration

Erika Droogsma received funding from the 'Wetenschapsfonds MCL' (science institute of the Medical Center Leeuwarden (MCL)) and Frision (the research foundation of the department of geriatric medicine of the MCL). For the remaining authors none were declared. The funding institutes had no role in study design, data collection, analysis, or interpretation or in preparation of the manuscript for publication.

Description of authors' roles

Erika Droogsma: conception and design of the study, data collection, analysis and interpretation of the data, writing of the manuscript.

Dieneke van Asselt: conception and design of the study, interpretation of the data and review and critique of the manuscript.

Marjolein Diekhuis: data collection, analysis and interpretation of the data and review and critique of the manuscript.

Nic Veeger: analysis and interpretation of the data and review and critique of the manuscript.

Cornelis van der Hooft: interpretation of the data and review and critique of the manuscript.

Peter Paul De Deyn: interpretation of the data and review and critique of the manuscript.

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Figure and table legends

Table 1. Patients characteristics at baseline

Table 2. Patient characteristics at baseline: patients included in the repeated measuresanalyses versus patients who could not be included in the repeated measures analyses, respectively responders versus non-responders

Table 3. Dosage of galantamine: responders versus non-responders

Table 4. Course of cognition (MMSE): responders versus non-responders (results from the repeated measures analysis)

Figure 1. Course of cognition described by changes in the Mini Mental State Examination (MMSE)

(a) Course of the MMSE for responders and non-responders from the Frisian Alzheimer's Disease Cohort

(b) Course of the MMSE for patients from the Frisian Alzheimer's Disease Cohort (responders, non-responders and all patients) and for patients from historical pre-ChEI-era Alzheimer cohorts (Han *et al.,* 2000)