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Galantamine treatment in Alzheimer’s disease: response and long-term outcome in a routine clinical setting

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Background: In the absence of long-term, placebo-controlled studies of cholinesterase inhibitors in Alzheimer’s disease (AD), analysis of the results of open-label trials becomes crucial. This study aimed to explore the three-year effects of galantamine treatment, as well as subgroups of response and adherence to treatment.

Methods: Two hundred and eighty patients with a clinical diagnosis of AD were included in the prospective, open-label, multicenter Swedish Alzheimer Treatment Study, and received galantamine treatment. Efficacy measures included cognitive tests, ie, the Mini-Mental State Examination (MMSE) and Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-cog), functional rating (Instrumental Activities of Daily Living Scale [IADL]), and global rating. Assessments were carried out before treatment and every six months for a period of three years. K-means cluster analysis was used to identify response subgroups.

Results: After three years of treatment, the mean change from baseline was 2.6 points in MMSE and 5.6 points in ADAS-cog scores. Globally, half of the patients improved or remained unchanged for two years. Cluster analysis identified two response clusters. Cluster 1 included patients with low ability in ADAS-cog and IADL scores at baseline. Even though the patients in cluster 1 were older and less educated, they responded better at six months compared with patients in cluster 2. Cluster 2 included patients with better ADAS-cog and IADL scores at baseline. Patients in cluster 2 had a higher frequency of the APOE ε4 allele, a slower pretreatment progression rate, and remained in the study longer than those in cluster 1. Three-year completers (n = 129, 46%) received higher doses of galantamine compared with dropouts.

Conclusion: AD patients who received long-term galantamine treatment were cognitively and globally stabilized. Subgroup response analysis identified a better short-term response in older patients with lower cognitive and functional abilities at baseline, a faster pretreatment progression rate, and a lower incidence of the APOE ε4 allele. The galantamine dose was higher in the population of completers.

Keywords: Alzheimer’s disease, long-term treatment, routine setting, cholinesterase inhibitor, galantamine, k-means cluster analysis, completion rates

Introduction
Alzheimer’s disease (AD) is the major cause of dementia, and underlies more than 60% of dementia cases. The incidence and prevalence of AD increase with age. Reports of increasing life expectancy in developed countries indicate that AD will be one of the biggest health care challenges in the future. Without treatment, AD is characterized by a progressive and irreversible decline in cognitive and practical abilities, leading to major difficulties after only a few years of disease duration.
In the 1990s, cholinesterase inhibitors (ChEIs) became the first drugs used to treat the symptoms of AD. ChEIs, which work by counteracting cholinergic deficits, and memantine, which inhibits glutamate overexpression, continue to be the drugs available for the treatment of AD. The second-generation ChEIs include donepezil, rivastigmine, and galantamine. Galantamine, which is a competitive and rapidly reversible inhibitor of acetylcholinesterase and an allosteric modulator of nicotine receptors, gained approval in Sweden in 2000. Multiple double-blind, placebo-controlled clinical trials showed the beneficial effects of galantamine treatment on the cognitive and behavioral symptoms in AD patients for up to six months. Because ethical constraints prohibit the use of long-term, placebo-controlled studies of ChEIs in AD, the analysis of results from open-label, long-term trials is important.

The response to ChEI varies within the AD population. Multiple factors have been outlined that enhance response to ChEI treatment in AD; however, there are no standard guidelines that define response to treatment. To overcome this issue, data-driven techniques, such as cluster analysis, could be used to investigate natural subgroups of AD populations in treatment studies. Low completion rates are another difficulty of long-term studies of AD patients, both with or without treatment. Three-year completion rates range between 4% and 39%, making it difficult to comprehend fully the long-term outcomes of treatment in AD. The investigation of treatment dropout and the search for methods aimed at enhancing completion rates and adherence to treatment are warranted in the field of AD research.

The Swedish Alzheimer Treatment Study was designed to evaluate the long-term effects of ChEI treatment in a routine clinical setting. Data obtained from patients treated with donepezil and rivastigmine were reported previously. The clinical outcome of and adherence to long-term galantamine treatment in a routine setting remain to be investigated.

In this report, we investigated the first 280 patients who received galantamine in the Swedish Alzheimer Treatment Study program; these individuals were recruited until the end of 2005 and had the opportunity to participate for three years. The aims of this report are to describe the cognitive (Mini-Mental State Examination [MMSE] and Alzheimer’s Disease Assessment Scale Cognitive Subscale [ADAS-cog]), functional (Instrumental Activities of Daily Living Scale [IADL]), and global outcomes of treatment, to identify treatment subgroups, and to investigate the rates of dropout and adherence to treatment.

Materials and methods

Subjects

Two hundred and eighty patients were recruited prospectively from 10 centers. The study data were collected by participating physicians at memory clinics across Sweden. The workup at baseline included medical history, informant-based information, physical and neurological examination, extended cognitive testing, laboratory tests, and computed tomography or magnetic resonance imaging of the brain. In some centers, patients were investigated additionally using cerebrospinal fluid taps, APOE genotyping, measurements of regional cerebral blood flow (SPECT), electroencephalography, and neuropsychological testing; however, these were not criteria for inclusion. Patients fulfilled the clinical criteria of dementia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and of probable or possible AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association.

The inclusion criteria were wide, and included AD patients aged older than 40 years, living at home at the time of diagnosis, having a caregiver, assessable via MMSE at baseline, and able to give their informed consent to participate in the study. Patients who did not fulfill the diagnostic criteria for AD and those already receiving active treatment with another ChEI or with contraindications to galantamine treatment were excluded from the study. The decision to start the patient on ChEI was made by the treating physician, in accordance with the standards used in routine clinical practice.

Medication other than antidementia drugs was allowed during the study. Concomitant medications and their doses were recorded. If other dementia treatments (ie, memantine or study drugs) were added, patients left the study at that point.

All participating centers were trained in Good Clinical Practice, in diagnostics, and in the uniform use of the rating scales applied in this study. The data from the different centers were collected prospectively and the results were sent continuously to the Memory Research Unit in Malmö for monitoring and data handling. The study was approved by the ethics committee of the University of Lund. All patients and their closest relative/caregiver provided written informed consent to participate in the study, which was carried out in accordance with the Declaration of Helsinki.

Study design and outcome measures

Cognitive assessment was performed using the MMSE and ADAS-cog (0–70). MMSE scores range from 0 to 30,
with a higher score indicating better function. Scores on the ADAS-cog version range from 0 to 70, with a higher score indicating lower function. ADAS-cog responses of patients at the different time intervals were investigated using the following cutoffs of change: “improved”, 4 or more points of improvement; “unchanged”, 3 to –3 points; and “worse”, 4 or more points of deterioration.

Functional status was measured using the IADL scale, which ranges from 8 to 31 points, with a higher value indicating more impaired function. The eight items on the IADL scale were telephone use, shopping, food preparation, housekeeping, laundry, transportation, medication, and finances. If an item was not applicable to the individual, its score was 0. Disease level at baseline was assessed using a seven-point scale (from “1 = normal” to “7 = very severe”). The Clinician’s Interview-Based Impression of Change (CIBIC) rating was used as a global measure of “change from baseline”. The CIBIC uses a seven-point scale (from “1 = very much improved” to “7 = very much worse”), with a score of 4 indicating no change from baseline. No guidelines or descriptors were provided to define the individual ratings. Global rating was meant to measure the overall improvement, regardless of patient score on cognitive tests. Patients could be regarded as being globally better but still score less well on the cognitive tests. The distinction between minimally improved or much improved was left to the clinical judgment of the individual rater.

Baseline was defined as the assessment prior to the first dose of treatment. All patients assessed at baseline and treated with at least one dose of galantamine were included in the outcome analysis (observed cases). The assessments at baseline were performed before and close to the start of ChEI treatment. Patients were assessed for all outcome measures at baseline and every six months after the baseline assessment for a period of three years. In addition, MMSE and global rating were performed at the two-month visit.

Comparative analysis

The Stern equation was used to calculate the annual change in ADAS-cog score if the patients had not been treated. This equation is based on the ADAS-cog (0–70) of AD patients with a baseline ADAS-cog score in the range of 5–69 points. The Stern equation is as follows:

\[
\text{Predicted ADAS-cog score at a time } T = -6.039689 + 1.329485 x_i - 0.005392 x_i^2 + (0.031974 + 0.036652 x_i - 0.000473634 x_i^2) T
\]

where \( T \) is time from baseline and \( x_i \) is baseline ADAS-cog score for an individual. The ADAS-cog value predicted using the Stern equation was calculated for each individual at each interval of the study. The mean change in ADAS-cog score from baseline was obtained based on these calculations. These scores were used as mathematical controls.

The annual decrease in MMSE score in untreated AD patients was estimated at 2–4 points per year, and the annual increase in ADAS-cog was estimated at 4–9 points per year, based on historical reports of annualized decline.

Subgroup analysis

A cluster analysis was applied to investigate the possibility of identifying natural subgroups of clinically sensible patients (short-term response). Patient baseline values of IADL and ADAS-cog and their six-month rate of change were used as variables in the analysis. The analysis included only patients with complete data at six months.

The subgroups identified were described and compared. Differences in age, gender, duration of illness, number of years of education, APOE genotype (presence or absence of the \( APOE \varepsilon 4 \) allele), number and type of medications at baseline, galantamine dose, occurrence of dropout, MMSE level at baseline, and pretreatment progression rate in MMSE were investigated. Pretreatment progression rate was calculated using the following formula: 30-baseline MMSE/estimated duration of symptoms in years, as described previously.

Treatment

After inclusion and baseline assessments, patients received galantamine treatment according to the approved product labeling, as in routine clinical practice. Patients were initially prescribed tablets, but when the extended-release capsules became available, patients switched to this formulation. All patients were started on a dose of 8 mg/day, which was increased to 16 mg/day after four weeks of treatment, aiming at a further dose increase to 24 mg/day. In some cases, the dose was reduced because of the presence of side effects. All decisions regarding dosage were left to the individual clinician, as in routine clinical practice, and all dosage adjustments were recorded throughout the study. The patients paid for their medication in accordance with the standards of the Swedish health care system.
poor effect/deterioration, somatic disease unrelated to galantamine treatment, add-on of memantine, entering another treatment study, and other reasons.

Predictors of dropout were investigated and included age, gender, duration of illness, number of years of education, APOE genotype (presence or absence of the APOE 4 allele), number of medications at baseline, type of medication at baseline, galantamine dose, and baseline MMSE, ADAS-cog, and IADL scores.

Statistical analysis

The SPSS program, version 17.0 (SPSS Inc, Chicago, IL) was used to perform the statistical analyses. The level of significance was set at \( P < 0.05 \) if not otherwise specified. Nonparametric methods were used to avoid the possibility of skewed distributions. The Mann–Whitney U test was applied if two independent groups were compared. The \( \chi^2 \) test was used to analyze nominal scale variables, eg, gender and APOE genotype.

The Wilcoxon signed-rank test was used to investigate differences in scores from the baseline to each assessment point. A logistic regression analysis using dropout (no/yes) as the dependent variable was applied to investigate predictors of discontinuation and their odds ratios.

A hierarchical cluster analysis using Ward’s method with squared Euclidean distance was applied to determine the adequate number of clusters. Agglomeration coefficients and dendrogram analysis displayed a two-cluster solution as the most optimal. Subsequently, a k-means cluster analysis with two clusters was applied using the baseline values of IADL, ADAS-cog, the six-month IADL scale, and ADAS-cog change from baseline as independent variables in the analysis.

Results

Subjects

The baseline characteristics of the 280 patients are displayed in Table 1. The mean age was 73.1 ± 8.2 years, and 62% of the patients were female. The median level of education was 9.8 ± 3.8 years. The mean duration of disease was 3.0 ± 1.7 years. At baseline, the mean MMSE score was 23.2 ± 4.1 and the ADAS-cog score was 16.8 ± 8.7. The mean baseline IADL score was 12.8 ± 5.2.

At baseline, 85% of the patients had concomitant medication (Table 1). The number of medications per person was 3.0 ± 2.7. The six groups of medication used by more than 10% of the study population are displayed in Table 1. The largest groups of medication were to treat vascular risk factors and included antihypertensive or cardiac therapy (38%), vitamins (B12 and/or folic acid, 32%), acetylsalicylic acid (29%), and lipid-lowering agents (18%). Medications for psychiatric symptoms included antidepressants (27%) and anxiolytics (13%). In addition 5%–9% of the patients used antidiabetic agents, analgesics (other than acetylsalicylic acid and nonsteroidal anti-inflammatory drugs), thyroid hormone therapy, and antacids and acid reducers. Less than 5% of the patients used antipsychotics, estrogen, nonsteroidal anti-inflammatory drugs, gingko/vitamin E, or asthma medication.

Table 1 Baseline characteristics and medication

<table>
<thead>
<tr>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
</tr>
<tr>
<td>Males/females %</td>
</tr>
<tr>
<td>Living status (%)</td>
</tr>
<tr>
<td>Living alone</td>
</tr>
<tr>
<td>Age at onset, years (range)</td>
</tr>
<tr>
<td>Age at baseline, years (range)</td>
</tr>
<tr>
<td>Illness duration at baseline, years</td>
</tr>
<tr>
<td>Years of education (range)</td>
</tr>
<tr>
<td>APOE 4 allele, carrier/noncarrier, n (%)</td>
</tr>
<tr>
<td>MMSE</td>
</tr>
<tr>
<td>ADAS-cog (0–70), mean (n)</td>
</tr>
<tr>
<td>IADL (n)</td>
</tr>
<tr>
<td>PSMS (range)</td>
</tr>
<tr>
<td>FAST (range)</td>
</tr>
<tr>
<td>Preprogression rate, MMSE decline/year</td>
</tr>
<tr>
<td>Medicationa n (%)</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Antihypertensives/cardiac therapy</td>
</tr>
<tr>
<td>Vitamins (folic acid, cobalamin)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
</tr>
<tr>
<td>Anxiolytics</td>
</tr>
</tbody>
</table>

Note: All baseline medications taken by more than 10% of the study population (n = 278), two patients did not provide baseline medication data.

Abbreviations: ADAS-cog, the Alzheimer’s Disease Assessment Scale-cognitive subscale; IADL, Instrumental Activities of Daily Living; SATS, Swedish Alzheimer Treatment Study; MMSE, Mini-Mental State Examination; SD, standard deviation; FAST, Functional Assessment Staging of Alzheimer’s Disease; PSMS, Physical Self-Maintenance Scale.

Study outcomes

Mini-Mental State Examination

The mean MMSE scores and the mean changes from baseline at the different visits are shown in Table 2. The mean MMSE score was 23.2 ± 4.1 at baseline and 21.7 ± 5.7 after 36 months. The MMSE score was significantly better at two months \( P < 0.001 \) and at six months \( P = 0.006 \) compared with baseline, and was stable at 12 months \( P = 0.616 \)
Table 2: Study overview

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>30 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on treatment (n)</td>
<td>280</td>
<td>280</td>
<td>267</td>
<td>242</td>
<td>220</td>
<td>192</td>
<td>152</td>
<td>129</td>
</tr>
<tr>
<td>Completion rate (%)</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
<td>86%</td>
<td>78%</td>
<td>69%</td>
<td>54%</td>
<td>46%</td>
</tr>
<tr>
<td>Mean galantamine dose, mg/day</td>
<td>14.5 ± 4.5</td>
<td>17.2 ± 4.0</td>
<td>18.4 ± 4.2</td>
<td>19.0 ± 4.5</td>
<td>18.9 ± 4.4</td>
<td>19.1 ± 4.3</td>
<td>19.4 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>MMSE, mean ± SD (n)</td>
<td>23.17 ± 4.14</td>
<td>23.95 ± 4.08</td>
<td>23.63 ± 4.41</td>
<td>23.28 ± 4.88</td>
<td>22.39 ± 5.14</td>
<td>21.91 ± 6.01</td>
<td>22.17 ± 5.27</td>
<td>21.74 ± 5.68</td>
</tr>
<tr>
<td>MMSE change from baseline,</td>
<td>0.79 ± 2.40</td>
<td>0.53 ± 2.74</td>
<td>−0.19 ± 2.93</td>
<td>−1.04 ± 3.46</td>
<td>−1.79 ± 4.34</td>
<td>−2.00 ± 3.86</td>
<td>−2.57 ± 4.08</td>
<td></td>
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<tr>
<td>mean, 95% CI</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>(n)</td>
<td>(280)</td>
<td>(244)</td>
<td>(223)</td>
<td>(191)</td>
<td>(174)</td>
<td>(131)</td>
<td>(125)</td>
<td></td>
</tr>
<tr>
<td>ADAS-cog change from baseline,</td>
<td>0.16 ± 4.77</td>
<td>−1.50 ± 6.17</td>
<td>−3.13 ± 7.66</td>
<td>−3.45 ± 7.55</td>
<td>−4.08 ± 8.02</td>
<td>−5.56 ± 10.08</td>
<td></td>
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<tr>
<td>mean ± SD</td>
<td></td>
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<tr>
<td>ADAS-cog change, Stern</td>
<td>−0.36 ± 2.00</td>
<td>−3.08 ± 2.84</td>
<td>−5.67 ± 3.85</td>
<td>−7.61 ± 4.68</td>
<td>−10.27 ± 5.48</td>
<td>−12.58 ± 2.27</td>
<td></td>
<td></td>
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<tr>
<td>equation, mean ± SD</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CIBIC, stable or better than baseline, %</td>
<td>93%</td>
<td>82%</td>
<td>69%</td>
<td>57%</td>
<td>50%</td>
<td>44%</td>
<td>41%</td>
<td></td>
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<tr>
<td>(263)</td>
<td></td>
<td>(231)</td>
<td>(211)</td>
<td>(180)</td>
<td>(174)</td>
<td>(126)</td>
<td>(119)</td>
<td></td>
</tr>
<tr>
<td>IADL change from baseline, SD</td>
<td>−1.26 ± 3.10</td>
<td>−2.01 ± 4.23</td>
<td>−3.26 ± 4.76</td>
<td>−3.85 ± 4.87</td>
<td>−4.57 ± 5.16</td>
<td>−5.28 ± 5.55</td>
<td></td>
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<tr>
<td>PSMS, change from baseline, SD</td>
<td>−0.36 ± 1.42</td>
<td>−0.62 ± 1.80</td>
<td>−1.13 ± 2.45</td>
<td>−1.21 ± 2.25</td>
<td>−1.43 ± 2.43</td>
<td>−1.65 ± 2.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAST, change from baseline, SD</td>
<td>−0.15 ± 0.075</td>
<td>−0.32 ± 1.02</td>
<td>−0.69 ± 1.19</td>
<td>−0.89 ± 1.49</td>
<td>−0.92 ± 1.53</td>
<td>−0.98 ± 1.78</td>
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</tbody>
</table>

Notes: ADAS-cog assesses cognitive function on a scale from 0–70, where a higher score indicates more severe dysfunction; MMSE assesses cognitive function on a scale from 0–30, where a lower score indicates more severe dysfunction. For clarity, clinical improvements in both scales are tabulated as a positive change from baseline, as have all the other measures.

Abbreviations: ADAS-cog, the Alzheimer’s Disease Assessment Scale-cognitive subscale; CI, confidence interval; IADL, Instrumental Activities of Daily Living; SATS, Swedish Alzheimer Treatment Study; MMSE, Mini-Mental State Examination; SD, standard deviation; FAST, Functional Assessment Staging of Alzheimer’s Disease; PSMS, Physical Self-Maintenance Scale; CIBIC, Clinician’s Interview Based Impression of Change.
compared with baseline (Wilcoxon signed-rank test). However, it deteriorated after this time point. The MMSE changes from baseline over time are depicted in Figure 1 and Table 2. The total mean decline in MMSE score from baseline after three years of treatment was 2.6 ± 4.1. This three-year result was in accordance with the results described previously for one year (2–4-point change) in historical cohorts of untreated patients.32,35,36

Alzheimer’s Disease Assessment Scale-cognitive subscale

The mean ADAS-cog scores and their mean changes from baseline are presented in Table 2. The mean ADAS-cog (0–70) score was 16.8 ± 8.7 at baseline and 19.4 ± 12.6 after 36 months of treatment. The ADAS-cog (0–70) changes from baseline over time are described in Figure 2. The total change in ADAS-cog score after three years of treatment was 5.6 ± 10.1 points above the baseline values. This was significantly better than the expected change in ADAS-cog of 12.6 ± 6.2, as calculated using the Stern equation (Table 2 and Figure 2). Furthermore, it was better than the expected annual decline of 4–8 points recorded in untreated historical cohorts.30,37 The ADAS-cog scores at six months were not different from those recorded at the baseline (stable, \( P = 0.248 \), Wilcoxon signed-rank test), but deteriorated after that. ADAS-cog responses at all time intervals (which were defined as “improved”, 4 or more points improvement; “unchanged”, 3 to -3 points of variation; and “worse”, 4 points or more of deterioration) are displayed in Figure 3B.

Instrumental Activities of Daily Living

Mean IADL scores and their changes from the baseline are presented in Table 2. The IADL scores deteriorated compared with baseline at all time points (Wilcoxon signed-rank test). However, it deteriorated after this time point. The MMSE changes from baseline over time are depicted in Figure 1 and Table 2. The total mean decline in MMSE score from baseline after three years of treatment was 2.6 ± 4.1. This three-year result was in accordance with the results described previously for one year (2–4-point change) in historical cohorts of untreated patients.32,35,36

Clinician’s Interview Based Impression of Change

The mean CIBIC scores are displayed in Table 2. In summary, three groups were defined based on the CIBIC ratings. A CIBIC score of 1–3 was considered as “improved”, a CIBIC score of 4 was considered “unchanged”, and a CIBIC score of 5–7 as “worse”. At two months, 93% of the patients remaining in the study were “improved or unchanged” at months 6, 12, 24, and 36; 81%, 69%, 50% and 41% of the patients were “improved or unchanged”, respectively (Figure 3A).

Subgroup analysis

A dendrogram hierarchical cluster analysis (Ward’s method) suggested a two-cluster solution. Cluster 1 was composed of 76 patients with a baseline IADL level of 16.9 ± 5.3 points, an ADAS-cog score of 25.9 ± 6.5 points, and a six-month ADAS-cog improvement from baseline of 2.0 ± 5.5 points. Cluster 2 was composed of 147 patients with a baseline IADL level of 10.3 ± 3.4 points, an ADAS-cog score of 11.4 ± 4.0 points, and a six-month ADAS-cog deterioration from baseline of 0.77 ± 4.2 points (Table 3). Patients in cluster 1 were significantly older at baseline (\( P = 0.002 \)) and at onset (\( P = 0.003 \)) had a worse MMSE level at baseline (\( P < 0.001 \)), exhibited a faster pretreatment progression rate (\( P < 0.001 \)), and were more prone to dropout from the study (\( P < 0.001 \)) than the patients in cluster 2. Patients in cluster 2 had a higher frequency of the APOE ε4 allele (\( P = 0.027 \)) and a higher level of education (\( P = 0.007 \)) than the patients in cluster 1. The patients in the two clusters did not differ regarding gender, dose of galantamine, number of medications at baseline, or disease duration (Table 3).
Patients in cluster 2 received significantly more lipid-lowering medication than patients in cluster 1 ($P = 0.019$); otherwise, the type of medication did not differ between the two clusters (Table 3).

Patients not included in the cluster analyses because of missing data ($n = 59$) were treated with a lower dose of galantamine ($14.1 \pm 4.1$ mg) compared with the patients who provided data for the cluster analysis ($16.0 \pm 3.1$ mg). However, they did not differ from the patients included in the cluster analyses regarding any of the other aspects mentioned above.

**Treatment**

The mean dose of galantamine was $15.6 \pm 3.4$ mg, and the mean doses of galantamine administered at the different time points are displayed in Table 2.
The baseline characteristics of the completers and non-completers of the present study were compared. Patients who left the study during the three-year interval had a significantly higher baseline ADAS-cog score ($P < 0.001$), a lower MMSE score ($P < 0.001$), and a higher IADL score ($P < 0.001$) compared with patients who remained in the study, thus indicating a more severe disease level. Moreover, the mean galantamine dose administered to noncompleters was lower (16.5 ± 4.6 mg) compared with that administered to completers (18.0 ± 3.1 mg; $P < 0.004$). The dropouts did not differ in number of medications at baseline, age at onset, age at baseline, duration of illness, education in years, gender, or APOE genotype compared with patients who completed the three years of the study. No differences in medication profiles at baseline were observed regarding use of any of the medication groups between the dropouts and completers. Similar results were obtained using a logistic regression model. A higher MMSE score at baseline ($P < 0.001$; odds ratio, 0.857) reduced the risk of dropout by 14.3% per MMSE point increase. Moreover, a higher dose of galantamine ($P < 0.001$; odds ratio, 0.81) reduced the risk of discontinuation by 19% for every milligram increase in galantamine dose. However, age, IADL at baseline, APOE genotype, years of education, and number of medications did not influence dropout.

**Discussion**

AD patients treated with galantamine in a routine clinical setting exhibited cognitive stabilization for up to one year after the onset of treatment. After three years of treatment, the mean MMSE change from baseline was 2.6 points. Subgroup response was assessed using cluster analyses, and two stable clusters were identified. Patients with higher age, lower cognitive and functional ability at baseline, faster pretreatment progression rate, and lower frequency of the APOE ε4 allele exhibited a better short-term response to treatment, but dropped out earlier. Moreover, a high adherence to treatment was observed compared with that reported by earlier studies, and the three-year completers received higher galantamine doses than the noncompleters.

The routine clinical setting, which renders our results relevant also for the “ordinary” AD patient, was one of the advantages of the present study. This is especially important because the highly selected cohorts used in placebo-controlled studies.
The response to ChEI treatment varies among the AD population. AD is a heterogeneous condition, and it is likely that the efficacy of various therapies differs among subgroups. This can depend not only on the medication used, but also on factors influencing disease progression (“how fast”) or disease severity (“how far”). Severity of disease and fast progression rate predict a positive short-term response to ChEI treatment in AD. However, the existence of malignant forms of AD with a fast progression rate and a lack of short-term response to ChEI treatment has also been reported. The definition of treatment response therefore remains difficult. There are no standard guidelines to describe response to treatment, and different definitions of response have been used previously. To overcome these difficulties in response definition, data-driven techniques, such as cluster analysis, may be better suited to the investigation of natural subgroups in AD treatment studies. Rockwood et al applied a cluster analysis to define outcome groups among a three-year completer population of AD patients. In the study presented here, we included not only the completer population, but all patients who provided at least six months of data. A stable two-cluster model was obtained, with different responses and characteristics. In our model, the response defined by the cluster analysis showed that patients exhibiting a better response at six months (cluster 1, n = 76) had lower baseline ADAS-cog and IADL scores and a faster pretreatment progression rate, which was in line with earlier observations using other response definitions. The calculated estimation of pretreatment progression rate yielded the same predictive response (faster pretreatment progression/better short-term response) as that described in earlier cohorts for which pretreatment progression rate was measured, rather than being calculated. Analysis of the differences between dropouts and completers of the present study showed that the three-year completers had less advanced disease at baseline and received higher doses of galantamine than the noncompleters. Low doses of ChEIs have been associated with early discontinuation and some studies showed that higher ChEI doses enhance short-term response. These results stress the importance of using adequate ChEI doses in AD treatment to enhance adherence and response to treatment. Patients in cluster 2 dropped out to a lesser extent than patients in cluster 1. However, these two clusters did not differ in galantamine dose, but patients in cluster 2 were treated with lipid-lowering medication at baseline to a greater extent than patients in cluster 1. A protective effect of this medication cannot be ruled out, but this remains to be explored further using larger cohorts.
In our cohort, 27% of patients were medicated with antidepressants at baseline, ie, before inclusion in the study. This figure is not high in naturalistic cohorts, because several studies show that AD patients have a large comorbidity with depression, ranging from 20% to 30%. Among large European naturalistic AD cohorts, a 24% depression rate was described in one study\(^4\) and in another study antidepressants were prescribed to 34% of the patients.\(^4\) We know that the patients receiving antidepressants at baseline did not drop out to a greater extent than the ones without this treatment.

High dropout rates are a problem in all long-term AD studies. Appendix 1 provides an overview of dropouts in various long-term studies to highlight this issue. Three-year completion rates of 4%–39% are reported. Thus, the three-year completion rate of 46% obtained in the current study is high compared with that of other long-term AD studies. In the present study, the two major reasons for dropout were addition of memantine or recruitment of patients to other treatment studies. As new treatment options emerged, patients were free to leave the present study to try other options. We do not know at this point whether these patients would have contributed to a different outcome if they had remained in the present study for the three-year period. We know that they were younger and better educated (data not shown), but did not differ in MMSE or ADAS-cog scores at baseline from the other dropout groups (data not shown). However, the possibility that patient deterioration was one of the reasons for adding memantine cannot be ruled out.

A recent observational health database study revealed that only 54% of patients receiving galantamine continued to do so for one year,\(^4\) which was longer than that observed for the donepezil-treated and rivastigmine-treated patients included in the same survey. Enhancement of the completion rates in long-term AD studies will be crucial in future studies of protective treatments, because these must be performed on a long-term basis.

**Conclusion**

Long-term galantamine treatment in a routine clinical setting resulted in stabilization of cognitive and global decline in AD patients. Moreover, after two years of treatment, half of the patients showed cognitive and global stabilization of their condition. We identified subgroups of patients with differential responses to treatment and dropout. The Swedish Alzheimer Treatment Study protocol used in this clinical setting may have contributed to the high completion rates observed in this study.

**Acknowledgments**

These data are presented on behalf of the Swedish Alzheimer Treatment Study Group steering committee, the members of which are outlined in Appendix 2. We wish to thank all the patients and their relatives who participated in this study. The authors are grateful to Daniel Ehinger for secretarial work, and to our research nurses, Cecilia Dahl, Annacarin Björkman, Yvonne Sjöberg, Tarja Tikkanen, and Eva Falk Langebro. We also wish to thank the staff of the different centers who participated in the management of the patients included in the study. This work was supported by grants from the Alzheimer Foundation, Sweden. Independent grants were received from Janssen-Cilag.

**Disclosure**

AKW has received speaker honoraria from Janssen-Cilag. CW has no disclosures to report. LM is a member of the advisory board at Pfizer AB, Sweden, and has received speaker honoraria from Pfizer.

**References**


Appendix 1

Completion rates in long-term studies of Alzheimer’s disease

<table>
<thead>
<tr>
<th>MMSE (mean) baseline level</th>
<th>Baseline (n)</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohs et al54 (don)</td>
<td>17.1</td>
<td>431</td>
<td>26%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winblad et al33 (don)</td>
<td>19.4</td>
<td>286</td>
<td>67%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Courtney et al19 (AD2000, don)</td>
<td>19 (median)</td>
<td>565</td>
<td>52%</td>
<td>20%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized controlled trials with open-label extensions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rogers et al14 (don)</td>
<td>27 (mean ADAS-cog)</td>
<td>133</td>
<td>75%</td>
<td>29%</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Doody et al10 (don)</td>
<td>763</td>
<td>75%</td>
<td>48%</td>
<td>7%4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grossberg et al11 (riv)</td>
<td>19.4</td>
<td>2010</td>
<td>74%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirillo et al13 (gal)</td>
<td>19.4</td>
<td>1039</td>
<td>47%</td>
<td>30%4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small et al14 (riv)</td>
<td>19.3</td>
<td>1998</td>
<td>74%</td>
<td>52%</td>
<td>33%</td>
<td>15%</td>
</tr>
<tr>
<td>Winblad et al13 (don)</td>
<td>19.4</td>
<td>286</td>
<td>67%</td>
<td>49%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td><strong>Open studies from naturalistic settings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minthon et al18 SATS (riv)</td>
<td>22.9</td>
<td>217</td>
<td>89%</td>
<td>66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallin et al19 SATS (don)</td>
<td>22.0</td>
<td>435</td>
<td>82%</td>
<td>60%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Lyle et al18 (don)</td>
<td>18.8</td>
<td>88</td>
<td>57%</td>
<td>43%</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Rascchetti et al15 (don, riv, gal)</td>
<td>18.2</td>
<td>5462</td>
<td>52%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wallin et al19 (tacrine)</td>
<td>20.5</td>
<td>50</td>
<td>66%</td>
<td>46%</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Without treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holmes and Lovestone17 (no treatment)</td>
<td>17.0</td>
<td>151</td>
<td>66%</td>
<td>44%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td><strong>Head-to-head studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bullock et al15 (riv, don)</td>
<td>994</td>
<td>994</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Multiple washout periods; 161 patients entered 12-week randomized controlled trial, 2 weeks washout, 133 entered open phase; 3-week or 6-week washout periods before open-label study started; 2.8 years; 64% of 12-month completers, continuous 24 mg galantamine treatment; 9 nine months.

Abbreviations: ADAS-cog, the Alzheimer’s Disease Assessment Scale-cognitive subscale; don, donezepil; riv, rivastigmine; gal, galantamine; SATS, Swedish Alzheimer Treatment Study; MMSE, Mini-Mental State Examination.

Appendix 2

The Swedish Alzheimer Treatment Study Group steering committee

Lennart Minthon (principal investigator), Niels Andreasen, Sture Eriksson, Annacarin Björkman (study coordinators); Lennart Minthon, Åsa Wallin, Carina Wattmo, Annacarin Björkman, Cecilia Dahl, Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Malmö; Stellan Båtsman, Anett Wunsch, Department of Primary Care, Kalix; Maria Eriksdotter Jönhagen, Niels Andreasen, Christina Sjödin, Department of Neurotec, Section Clinical Geriatrics, Karolinska Institutet, Alzheimer’s Disease Research Center, Karolinska University Hospital, Huddinge, Stockholm; Sture Eriksson, Birgitta Näsman, Liselotte Mannberg, Department of Community Medicine and Rehabilitation, Umeå University, Umeå; Michaela Grut, Marie Rydén, Eva Mohlin, Department of Geriatric Medicine, Cognitive Section, Danderyd Hospital, Danderyd; Anders Wallin, Mikael Jonsson, Kerstin Gustavsson, Institute of Clinical Neuroscience, Göteborg University, Göteborg; Hasse Olofsson, Berit Holm, Memory Clinic Uddevalla Hospital, Uddevalla; Anders Nelvig, Cathrin Viklund, Geriatric Clinic, Sundsvall Hospital, Sundsvall; Torgny Jarl, Maria Könberg, Geriatric Clinic, Härnösands Hospital, Härnösand; Kristina Are, Birgitta Liffner, Carina Borén, Department of Geriatric Falköpings Hospital, Falköping, Sweden.

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