Response of Patients With Alzheimer Disease to Rivastigmine Treatment Is Predicted by the Rate of Disease Progression

Martin R. Farlow, MD; Ann Hake, MD; John Messina, PharmD; Richard Hartman, PhD; Jeffrey Veach, MS; Ravi Anand, MD

Background: Evidence suggests that disease severity predicts the response of patients with Alzheimer disease (AD) to cholinesterase inhibitor treatment, raising the question of whether disease progression also predicts response to this treatment.

Objective: To evaluate retrospectively whether rate of disease progression during placebo treatment affects response to subsequent rivastigmine tartrate therapy for patients with mild to moderately severe AD.

Design: A 26-week, open-label extension study following a 26-week, double-blind, randomized, placebo-controlled trial.

Setting: Outpatient research centers at 22 sites in the United States.

Patients: We studied 187 of 235 patients originally randomized to receive placebo treatment in the double-blind phase of the trial who continued with open-label (rivastigmine) extension therapy.

Intervention: Placebo treatment for 26 weeks followed by rivastigmine treatment, 2 to 12 mg/d, for 26 weeks.

Main Outcome Measures: Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-Cog), Progressive Deterioration Scale, Mini-Mental State Examination, and Global Deterioration Scale scores.

Results: Rivastigmine administration during open-label extension therapy benefited patients who had progressed slowly and those who had progressed rapidly during initial double-blind placebo treatment. Slowly progressive patients responded with a mean 1.03-point improvement in the week 26 (ie, start of open-label rivastigmine treatment) ADAS-Cog score at 12 weeks of rivastigmine treatment (week 38 of treatment; P = .02 vs week 26). However, more rapidly progressive patients had a significantly larger mean 4.97-point improvement from the week 26 ADAS-Cog score at 12 weeks (with respect to week 26 of treatment and slowly progressive patient scores, P < .001 for both). Thus, a more rapid disease progression rate while receiving placebo treatment was predictive of a significantly stronger patient response to rivastigmine therapy. This relation also was observed with the other 3 outcome measures and was still apparent when accounting for disease severity.

Conclusions: Rate of disease progression for patients with mild to moderate AD seems to predict response to rivastigmine treatment. Patients with more rapidly progressive disease might be particularly likely to benefit from rivastigmine therapy.

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Alzheimer disease (AD), the most common form of dementia, affects up to 6% of the US population older than 65 years1,2 and is heterogeneous in its clinical presentation, including the rate of disease progression. Investigators have described slowly progressive and rapidly progressive forms of the disease,3,4 suggesting that there might be considerable variation in the disease process or in the patient’s vulnerability to the illness.

To determine prognosis for an illness such as AD, in which there is a continuous neurodegenerative process, it is useful to assess how rapidly the disease is progressing clinically and how severely the patient is currently affected. The issue of which factor best predicts the course of AD—rate of disease progression vs disease severity (ie, “how fast” vs “how far”)—has been the focus of much investigation.5-8 Although rate of disease progression and disease severity seem to be predictive of disease course, rate of progression might be more important than disease severity in determining prognosis.9

Historically, AD severity was defined most often by the degree of cognitive im-
PATIENTS AND METHODS

STUDY DESIGN AND PATIENTS

This was a 26-week, open-label extension study following a 26-week, double-blind, randomized, placebo-controlled, parallel group trial of 2 dose levels of rivastigmine for treatment of patients with mild to moderately severe AD.

Patients were enrolled in the double-blind study according to inclusion and exclusion criteria described previously. These patients had the option to continue into the open-label extension study if they had returned for scheduled efficacy evaluations at week 26 of the double-blind trial. Of 235 patients originally enrolled in the 26-week double-blind study and randomized to receive placebo treatment, 187 (80%) continued into the 26-week open-label extension study and are the subject of this retrospective analysis. All procedures were performed in accordance with the ethical standards of the institutional committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 1983.

RIVASTIGMINE TREATMENT

During open-label treatment with rivastigmine, investigators and patients remained masked to the patient's original treatment assignment (ie, placebo or 1 of 2 dose levels of rivastigmine) in the preceding double-blind trial.

The morning after the last office visit of the double-blind trial, patients began open-label rivastigmine (1 mg twice daily) treatment and had their dose flexibly titrated (at a rate of 1 mg twice daily per week) to a maximum tolerated dose of up to 6 mg twice daily.

ASSESSMENTS OF TREATMENT RESPONSE

Patient response to open-label rivastigmine treatment was evaluated using 4 instruments that assessed patient cognitive, function in performing activities of daily living, and disease severity. The ADAS-Cog is a 70-point scale used to evaluate patients cognitively and function in performing activities of daily living, and to assess the degree of impairment in cognitive, self-care activities, and the ability to perform activities of daily living, with a score of 7 representing severe cognitive impairment. The ADAS-Cog is a 7-point scale that measures the degree of impairment in cognitive performance, with a score of 30 representing “normal” cognitive performance. The GDS is a 7-point scale that measures the degree of impairment in instrumental activities of daily living, is a 100-point bipolar visual analogue scale that, based on caregiver input, measures the ability of patients to perform various activities of differing complexity. A higher score represents better functional ability, and a positive change from the baseline score reflects an improvement; PDS scores were evaluated at week 26 (ie, the start of open-label treatment) and at weeks 38, 44, and 52 of treatment or at early termination.

The PDS, an evaluation of performance of basic and instrumental activities of daily living, is a 100-point bipolar visual analogue scale that, based on caregiver input, measures the ability of patients to perform various activities of differing complexity. A higher score represents better functional ability, and a positive change from the baseline score reflects an improvement; PDS scores were evaluated at week 26 (ie, the start of open-label treatment) and at weeks 38, 44, and 52 of treatment or at early termination.

In assessing the relation between rate of progression and treatment response, 2 types of analyses were performed. First, patients were classified with respect to disease progression as being “slow” vs “rapid” based on the magnitude of change seen during 26-week double-blind placebo treatment. Patients were classified separately with respect to change in their ADAS-Cog and PDS scores.

The ADAS-Cog and PDS scores were chosen as the basis for progression classification because they measure cognitive and functional changes, respectively, with both of these domains having been used in the past to measure disease progression. Untreated patients decline at an average annual rate of approximately 6 to 12 points on the ADAS-Cog. Moreover, a 4-point change in the ADAS-Cog score and a 10% change in the PDS score are considered clinically meaningful. These 2 groups of patients were compared using an analysis of variance model. This model was fit with (2-way model with progression and sex as factors) and without (1-way model with progression as a factor) sex covariates for age and baseline score. The 2-way analysis of covariance was performed to assess the robustness of any effect after adjusting for sex, age, and baseline score. Simple linear regression models also were fit to assess the linear relation between the “change from baseline score at the end of 26-week placebo treatment” and the “change from week 26 assessment score.” In addition, multiple linear regression was used to assess the effect of the change from baseline score at the end of 26-week placebo treatment in the presence of baseline disease severity.

For all analyses, nominal P<.05 determined statistical significance.

In this regard, instruments such as the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-Cog) and the Mini-Mental State Examination (MMSE) were used to provide a measure of cognitive impairment. However, it has been recognized that the degree of functional impairment also reflects AD severity. The Global Deterioration Scale (GDS) was designed specifically to evaluate AD severity by measuring cognitive and functional performance. In addition, scores on an instrument such as the Progressive Deterioration Scale (PDS) also provide an index of disease severity; they reflect the ability of the patient with AD to perform specific instrumental and basic activities of daily living, which become increasingly compromised as the disease progresses.

The inhibition of cholinesterase (ChE), the enzyme responsible for acetylcholine catabolism, is the most
Rapidly Progressive Patients

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These sequential trials have allowed for evaluation of patients initially treated for 26 weeks with placebo, who may have declined at a slower or faster rate during this period, and subsequently treated with rivastigmine for 26 weeks.

The objective of this study was to analyze retrospectively the data obtained from the 2 sequential rivastigmine trials (double-blind study B352 and open-label study B353) to evaluate the relation between the underlying rate of disease progression for patients with mild to moderately severe AD and the response to rivastigmine treatment.

Table 1. Demographic and Baseline Characteristics of Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Slowly Progressive Patients</th>
<th>Rapidly Progressive Patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADAS-Cog Score Decline†</td>
<td>PDS Score Decline†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 101)</td>
<td>(n = 102)</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (41)</td>
<td>43 (42)</td>
<td>84 (43)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (59)</td>
<td>59 (58)</td>
<td>119 (57)</td>
</tr>
<tr>
<td>Age, y, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>11 (11)</td>
<td>14 (14)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>66-75</td>
<td>42 (42)</td>
<td>35 (34)</td>
<td>77 (39)</td>
</tr>
<tr>
<td>76-85</td>
<td>45 (45)</td>
<td>52 (51)</td>
<td>97 (46)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>74.2 (45.0-89.0)</td>
<td>74.4 (45.0-87.0)</td>
<td>75.4 (55.0-87.0)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>93 (92)</td>
<td>95 (93)</td>
<td>188 (95)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (5)</td>
<td>4 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dementia duration, mean (range), mo</td>
<td>38.8 (6-144)</td>
<td>38.1 (6-144)</td>
<td>37.7 (6-180)</td>
</tr>
<tr>
<td>ADAS-Cog score, mean (SD)</td>
<td>17.9 (8.9)</td>
<td>19.0 (9.4)</td>
<td>24.4 (11.2)</td>
</tr>
<tr>
<td>PDS score, mean (SD)</td>
<td>60.9 (17.8)</td>
<td>59.1 (17.9)</td>
<td>50.9 (15.4)</td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>21.5 (3.9)</td>
<td>21.0 (4.2)</td>
<td>18.7 (4.6)</td>
</tr>
<tr>
<td>GDS score, mean (SD)</td>
<td>3.7 (0.9)</td>
<td>3.8 (0.8)</td>
<td>4.1 (0.8)</td>
</tr>
</tbody>
</table>

*Baseline refers to the start of the double-blind study (ie, the start of 52 weeks of treatment). ADAS-Cog indicates Alzheimer’s Disease Assessment Scale–cognitive subscale; PDS, Progressive Deterioration Scale; MMSE, Mini-Mental State Examination; and GDS, Global Deterioration Scale.
†The declines occurred during the preceding placebo treatment. For the definition of slowly and rapidly progressive patients based on the decline in ADAS-Cog and PDS scores, see the “Statistical Analyses” subsection of the “Patients and Methods” section.

Extensively studied and best developed therapeutic approach for the symptomatic treatment of AD, providing clinical benefit presumably through an increase in synaptic acetylcholine levels and enhanced cholinergic neurotransmission. Several attempts have been made to identify patient characteristics that may best predict the level of response to ChE inhibitor treatment, including disease severity, sex, and age. Substantial evidence suggests that patients with AD in the moderate stage, during which disease progression is known to be more rapid than during earlier stages, have a stronger response to ChE inhibitor therapy than do patients with AD in the mild stage. This finding raises the question of whether rate of disease progression also predicts treatment response.

Rivastigmine tartrate (ENA 713, Exelon; Novartis Pharmaceuticals Corp, East Hanover, NJ) is a ChE inhibitor of the carbamate type that inhibits acetylcholinesterase and butyrylcholinesterase and shows selectivity for the hippocampus and cortex, regions in which cholinergic deficits are most prominent in AD. In a 26-week study of rivastigmine treatment efficacy and safety in patients with AD (study B352, Novartis Pharmaceuticals Corp), patients were randomized to receive either rivastigmine or placebo treatment. Following 26 weeks of double-blind treatment, patients had the opportunity to continue into a 26-week open-label treatment phase (study B353, Novartis Pharmaceuticals Corp). These sequential trials have allowed for evaluation of patients initially treated for 26 weeks with placebo, who may have declined at a slower or faster rate during this period, and subsequently treated with rivastigmine for 26 weeks.

The demographic and baseline characteristics of the evaluated patients are summarized in Table 1. Patients categorized as being slowly or rapidly progressive based on less than a 4-point or a greater than or equal to a 4-point deterioration in the ADAS-Cog score, respectively, were comparable in age, distribution according to race and sex, and mean dementia duration. Similarly, categorization of patients as slowly or rapidly progressive based on less than a 10% or an equal to or greater than 10% deterioration in the PDS score, respectively, also did not reveal any substantial differences between the demographic characteristics of these patient groups.

Sixty-five percent of patients progressed to taking a mean rivastigmine dose of 6 to 12 mg/d during open-label treatment.

Of 187 patients enrolled in this open-label extension study, an average (based on the 2 outcome measures used to categorize rate of disease progression) of 26.5% of slowly progressive patients and 24.0% of rapidly progressive patients discontinued rivastigmine treatment. The most common reason for treatment discon-
Small sample sizes (n in body systems and specific adverse events, together with events recorded. The inconsistency of observations across all body systems assessed or all specific adverse events. However, this was not observed consistently.)

rapidly progressive patients, a greater proportion received rivastigmine, 6 to 12 mg/d, than receiving less than 6 mg/d tended to experience adverse events. In general, for slowly and rapidly progressive patients, a proportion receiving rivastigmine, 6 to 12 mg/d, than receiving less than 6 mg/d tended to experience adverse events (data not shown). However, this was not observed consistently across all body systems assessed or all specific adverse events recorded. The inconsistency of observations across body systems and specific adverse events, together with small sample sizes (n=14) in the less than 6 mg/d groups complicated any interpretation of a dose–adverse response relation. For slowly and rapidly progressive patients, the most frequently occurring adverse events were gastrointestinal in nature (data not shown).

**Figure 1.** Response of patients with Alzheimer disease to rivastigmine treatment based on their rate of disease progression as defined by the degree of deterioration in the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) score. Slowly progressive patients were defined by less than a 4-point deterioration in ADAS-Cog score during the preceding 26 weeks of placebo treatment. Rapidly progressive patients were defined by a 4-point or greater worsening in ADAS-Cog score during the preceding 26 weeks of placebo treatment. Sample sizes and mean±SE changes from the week 26 score were as follows: rapidly progressive patients—week 38: n=71, 4.97±0.83; week 44: n=68, 2.57±0.79; and week 52: n=65, 2.01±0.97; and slowly progressive patients—week 38: n=86, 1.03±0.44; week 44: n=82, −0.57±0.50; and week 52: n=78, −0.90±0.57). Asterisk indicates P<.05 compared with the week 26 (ie, the start of rivastigmine treatment) score; dagger, P<.05 compared with slowly progressive patients.

**Figure 2.** Response of patients with Alzheimer disease to rivastigmine treatment based on their rate of disease progression as defined by the degree of deterioration in the Progressive Deterioration Scale (PDS) score. Slowly progressive patients were defined by less than a 10% worsening in PDS score during the preceding 26 weeks of placebo treatment. Rapidly progressive patients were defined by at least a 10% or greater deterioration in PDS score during the preceding 26 weeks of placebo treatment. Sample sizes and mean±SE changes from the week 26 score were as follows: rapidly progressive patients—week 38: n=63, 0.07±1.06; week 44: n=62, −0.29±1.06; and week 52: n=59, 0.34±1.31; and slowly progressive patients—week 38: n=86, −2.74±0.72; week 44: n=80, −3.87±0.65; and week 52: n=78, −2.54±0.88). Asterisk indicates P<.05 compared with the week 26 (ie, the start of rivastigmine treatment) score; dagger, P<.05 compared with slowly progressive patients.

**RATE OF DISEASE PROGRESSION AND RESPONSE TO RIVASTIGMINE TREATMENT**

**Assessment Using the ADAS-Cog**

Responses to rivastigmine treatment as measured by the ADAS-Cog during weeks 26 to 52 for patients classified as slowly or rapidly progressive based on the change in ADAS-Cog score are depicted in **Figure 1**. Slowly progressive patients had a week 26 ADAS-Cog score that was significantly better than the week 26 ADAS-Cog score of rapidly progressive patients (17.5 vs 33.5; P<.001). Patients classified as being rapidly progressive exhibited a marked improvement from week 26, with a mean change of 4.97 points (P<.001) after 12 weeks of treatment (week 38 of study participation), a response that was significantly better than that observed for slowly progressive patients (P<.001). At subsequent points, ADAS-Cog scores for rapidly progressive patients declined but continued to show significant improvement from the week 26 value and remained significantly better than the scores for slowly progressive patients (Figure 1).

**Assessment Using the PDS**

Responses of patients classified as slowly or rapidly progressive based on change in PDS score were evaluated...
According to performance on the PDS (Figure 2), slowly progressive patients had a week 26 PDS score that was significantly better than the week 26 score of rapidly progressive patients (61.0 vs 38.5; \(P < .001\)). Rapidly progressive patients showed little change from the week 26 score during the study, whereas slowly progressive patients showed a significant worsening from the week 26 score at weeks 38, 44, and 52. Patients classified as rapidly progressive had significantly stronger responses to treatment than did slowly progressive patients at weeks 38 and 44 (Figure 2).

**Simple Linear Regression Analyses of the ADAS-Cog and PDS Data**

Results of linear regression analyses for weeks 38, 44, and 52 of treatment are summarized in Table 2. There was a statistically significant inverse relation between the magnitude of patient response to rivastigmine treatment and disease progression that was observed regardless of whether disease progression was defined by the rate of deterioration in ADAS-Cog score or by the rate of deterioration in PDS score.

**Covariate and Multiple Linear Regression Analyses**

Additional covariate analyses were performed to determine the effect, if any, of baseline assessment scores (ie, disease severity), sex, and age on the relation between patient response to rivastigmine treatment and rate of disease progression. Results of the ADAS-Cog and PDS covariate analyses were consistent with each other and showed that the relation between response to rivastigmine treatment and rate of disease progression was consistent with previous analyses that did not include baseline severity, sex, and age in the model.

Similarly, when the covariate analyses also included an adjustment for mean rivastigmine dose, response patterns similar to those described previously and presented in Figures 1 and 2 were observed over time for the ADAS-Cog and PDS scores, respectively (data not shown). Moreover, the relation between response to rivastigmine treatment and rate of disease progression remained statistically significant for these 2 treatment assessments (data not shown).

Multiple linear regression models showed that even after baseline disease severity was accounted for, change from baseline score at the end of 26 weeks of placebo treatment still significantly predicted magnitude of response to rivastigmine therapy (Table 2).

**Assessments Using the MMSE and the GDS**

Results of linear regression analyses using data derived from MMSE or GDS assessments were consistent with those obtained from analyses of the ADAS-Cog and PDS data. For the MMSE and the GDS, there was a statistically significant inverse relation between the response to 26 weeks of rivastigmine treatment and the degree of deterioration in the particular assessment score after placebo treatment (Table 2).

**Table 2. Linear Regression Analyses of Change From Week 26 Assessment Scores With Rivastigmine Treatment as a Function of Degree of Deterioration in These Scores After Placebo Treatment**

<table>
<thead>
<tr>
<th>Assessment Scale</th>
<th>Treatment Week*</th>
<th>(R^2)</th>
<th>Slope</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease Assessment Scale−cognitive subscale</td>
<td>38</td>
<td>0.133</td>
<td>−0.364</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>0.107</td>
<td>−0.325</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>0.092</td>
<td>−0.339</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Progressive Deterioration Scale</td>
<td>38</td>
<td>0.073</td>
<td>−0.190</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>0.071</td>
<td>−0.202</td>
<td>.001†</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>0.051</td>
<td>−0.184</td>
<td>.008†</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>52</td>
<td>0.100</td>
<td>−0.348</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Global Deterioration Scale</td>
<td>52</td>
<td>0.153</td>
<td>−0.381</td>
<td>&lt;.001†</td>
</tr>
</tbody>
</table>

* Treatment duration reflects the total treatment time. Patients received 26 weeks of placebo treatment followed by treatment with rivastigmine.
† Based on multiple linear regression adjusting for baseline severity.

The present retrospective analyses show that the magnitude of patient response to rivastigmine treatment may be predicted, at least in part, by the rate of disease progression preceding treatment. Patients with more rapid rates of disease progression manifested a significantly stronger response to rivastigmine treatment than did patients with a slower rate of disease progression. To our knowledge, this is the first study of a relation between patient response to ChE inhibitor treatment and rate of disease progression.

The relation between response to rivastigmine treatment and rate of disease progression was evaluated using 4 different assessments of patient response (ADAS-Cog, PDS, MMSE, and GDS) and 2 different statistical models (using progression as a categorical and linear predictor of response). A statistically significant inverse relation between response to rivastigmine treatment and rate of disease progression, in which a greater treatment response was predicted by a more rapid rate of disease progression, was consistently observed in all 4 assessments of treatment response. Furthermore, results of the analysis of variance and linear regression analyses (performed for ADAS-Cog and PDS assessments) were consistent. In addition, when disease severity, as defined by baseline assessment score, was accounted for in the covariate and multiple regression analyses, the relation between response to rivastigmine treatment and rate of disease progression remained statistically significant. Collectively, these findings constitute highly compelling evidence of a relation between the magnitude of the response to rivastigmine treatment and the rate of disease progression.
That the rate of disease progression before treatment seems to be a strong and selective predictor of response to ChE inhibitor therapy is reflected most dramatically by the ADAS-Cog data from this study. After 12 weeks of treatment with rivastigmine, patients classified as rapidly progressive demonstrated a 4.97-point improvement in ADAS-Cog score relative to the mean score at week 26.

It has been proposed that the rate of disease progression (i.e., how fast), as measured by the rate of cognitive or functional decline, may be more important than disease severity (i.e., how far) for predicting disease course and the time to certain end points such as nursing home placement or death. Data from the present analyses suggest that rate of disease progression may be valuable not only for establishing a prognosis but also for predicting the level of responsiveness of patients with AD to rivastigmine treatment and, possibly, to therapy with other ChE inhibitors.

Why some patients with AD decline more rapidly than others is not currently known. Several factors have been suggested to impact the rate of disease progression, including apolipoprotein E genotype, the early appearance of aphasia or apraxia, the presence of extrapyramidal signs or certain behavioral symptoms, and genetic factors. However, the relation of these factors to the underlying pathophysiological processes and components of the disease remains unclear. The rate of decline might reflect the cumulative effects of different neuropathological processes, including cholinergic cell loss, that may spread at widely differing rates in individual patients.

In summary, rivastigmine may have greater treatment effects in patients with more rapidly progressive disease. The relation between response to rivastigmine treatment and disease rate of decline was still apparent when accounting for disease severity. Whether patients with more rapidly progressive AD are more responsive to treatment with other ChE inhibitors or alternative interventional therapies remains to be determined and merits investigation in future studies.

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