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Plasma Aβ levels as predictors of response to rivastigmine treatment in Alzheimer's disease

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Abstract. Cholinesterase inhibitors are currently the mainstream of symptomatic treatment of patients with Alzheimer's disease. The response to treatment with cholinesterase inhibitors is clinically difficult to predict. Several demographic, clinical and biological variables have been proposed as pre-treatment predictors of long-term therapy efficacy. In this paper, consistently with previous reports, we confirm that higher initial disease severity and faster progression of cognitive impairment increase the chance of a clinically meaningful response to cholinesterase inhibitor therapy in a carefully selected population of patients with Alzheimer's disease. Moreover, for the first time we demonstrate the association between the increase in the concentration of plasma $A\beta_{1-42}$ peptide after 2 weeks of treatment with an initial dose of rivastigmine and the likelihood of a positive response to treatment after 6 months. A change in plasma $A\beta_{1-42}$ level might constitute a novel biochemical predictor of rivastigmine treatment efficacy in Alzheimer's disease.

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INTRODUCTION

Inhibitors of brain cholinesterase activity (cholinesterase inhibitors, ChEI) are currently the mainstream of symptomatic treatment of patients with mild to moderate dementia in the course of Alzheimer's disease (AD). In several pivotal studies their efficacy in correcting major cognitive deficits acquainted in AD has been proven with relatively good safety profile and usually benign adverse effects (Davis et al. 1992, Rogers et al. 1998, Rosler et al. 1999, Wilcock et al. 2000). However, the response to ChEI treatment is clinically difficult to predict and it seems that at least one third of treated subjects take no clinically meaningful advantage of these drugs. Moreover, mostly due to response heterogeneity, the weighted mean benefit of ChEI treatment is disappointingly modest (Lanctôt et al. 2003a, Ritchie et al. 2004) which even led some authors (Kaduszkiewicz et al. 2005) as well as authorities (NICE 2006) to put their clinical usefulness, rather undeservedly (Livingston and Katona 2000), in question.

A number of clinical features has been proposed as possible response predictors, including younger age, faster rate of progression, moderate rather than mild level of cognitive dysfunction, the presence of symptoms suggesting Lewy body pathology, concomitant vascular pathology and brain perfusion changes after testing dose as well as neuropsychological profile and an initial clinical response to treatment (Bullock et al. 2005, Farlow et al. 2001, Lanctôt et al. 2003b). Moreover, results of several studies suggest that more biological markers of response might be identified, such as apolipoprotein E and butyrylcholinesterase genotypes, pretreatment postural blood pressure drop, quantitative electroencephalography as well as SPECT, MRI and PET imaging results (for review see Lanctôt et al. 2003b).

Amyloid β peptides (Aβ), the products of an alternative protease cleavage of their precursor protein βAPP (amyloid precursor protein) are thought to be directly implicated in the pathogenesis of AD. In brief, the tendency of Aβ peptides to aggregate, their reported neurotoxicity, and genetic linkage studies, have led to a hypothesis of AD pathogenesis that many AD researchers term the amyloid cascade hypothesis. According to this model, an increased production of Aβ or the shift toward the generation of its longer isoform (42-43 rather than 40 residues) results in neurodegeneration and ultimately leads to dementia through a cascade of events that include oxidative stress, excessive intracellular calcium flow and apoptosis, neurovascular dysregulation and central cholinergic activity decline (Tanzi and Bertram 2005, Wilquet and De Strooper 2004).

Over the last several years a number of reports have emerged suggesting that at least some ChEI might take part in βAPP metabolism, influencing its secretion and Aβ differential cleavage. It has also been reported that the difference in action of metrifonate, physostigmine, phenserine and tacrine on APP processing is independent of their selectivity for the cholinesterase enzymes. This is possibly due to different targets employed by ChEI (Lahiri et al. 2000, Zhang 2004). Moreover, we (Sobów and Kloszewska 2005) and others (Basun et al. 2002, Zimmermann et al. 2005) have shown that the treatment with ChEI might influence βAPP metabolism in AD patients as measured by changes in plasma (including platelet-derived) metabolites. Interestingly, studies on CSF samples generally failed to show a significant effect that might indicate different sources of βAPP metabolites in CSF and plasma (Moriearty et al. 1999, Stefanova et al. 2003).

In our previous pilot study we have demonstrated that short-term treatment with ChEI rivastigmine exhibits a significant effect on plasma concentrations of $A\beta_{1-42}$ (mean increase after treatment reached 7.8 ± 8.4 pg/ml) with a negative correlation to patients age, while no changes in $A\beta_{1-40}$ levels were detected (Sobow and Kloszewska 2005). Here, we expand our preliminary observations using a larger sample of patients and present the results of a longitudinal observation of this cohort. The aim of the study was to confirm our pilot observations and to find out if the change of plasma Aβ levels after initial treatment might predict clinical response to treatment at 6 months. Additionally, several clinical variables (such as disease severity (as measured by ADAS-cog), disease progression rate, age at onset and others) as well as apolipoprotein E genotype were investigated as potential predictors of response to rivastigmine treatment within a 6-month observation period.

METHODS

Study population selection and psychometric assessments used

Patients heterogeneity and apparent subject-to-subject variation of results is a major problem of many AD clinical studies and the internationally recommended clinical criteria (e.g. DSM-IV, ICD-10 or NINCSD-ADRDA) are not specific enough to exclude patients with other than AD possible diagnoses. We have then employed a clinical

procedure to "enrich" our patients sample in "pure", late-onset (first detectable symptoms after 65 years of age) and non-familial (sporadic) AD. Of initially screened 106 patients fulfilling the working criteria of AD according to the NINCSD-ADRDA set, we have excluded 47 due to the following reasons: 19 also fulfilled ICD-10 criteria for mixed dementia of the Alzheimer's type, 9 also fulfilled the consensus criteria of dementia with Lewy bodies, 5 also fulfilled the Lund-Manchester criteria for frontotemporal dementia, 9 had a significant history of drug/alcohol misuse or dependence and, finally, 5 were classified as familial cases. Five subjects were *post-hoc* excluded from the final analyses as they did not finish the 6 month observation period. In 4 cases the reason of dropping out was poor rivastigmine tolerance and 1 patient was lost to follow-up.

Fifty four subjects (37 female, mean age 77.6 ± 4.4) satisfying criteria for mild (n=25) or moderate (n=29) dementia according to the Clinical Dementia Rating (CDR) scores were included in the study (compare Table I for baseline demographic characteristics of the study participants). All patients and their caregivers (when available) have agreed to participate in the study and signed an informed consent. The study has been accepted by the Medical University of Lodz Ethics Committee and all the procedures were evaluated as being in accord with The World Medical Association Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki: http://www.wma.net/e/policy/b3.htm).

Specifically, the decision of prescribing rivastigmine was based on clinical grounds only and patients treatment during the entire study was not influenced by the study protocol (e.g., drug discontinuation or switching to another drug or prescription of other drugs were allowed at any time point).

At baseline MMSE and Clock Drawing Test were used to screen for the presence of dementia and CDR for the estimation of severity. ADAS-cog (Alzheimer's Disease Assessment Scale – cognitive subscale) has been chosen as a general psychometric scale to assess treatment impact on cognitive deficits and patients were classified as responders at 6 months if the ADAS-cog score was at least 3 points lower as compared to baseline, as clinically stable if the ADAS-cog score was between –2 to +2 points as compared to baseline, and as non-responders if the ADAS-cog was at least 3 point higher as compared to baseline. The rationale for this classification system stemmed from the results of pivotal studies on ChEI, with the mean response advantage after 6 months of treatment was between 2 to 4 points (Davis et al. 1992, Rogers et al. 1998, Rosler et al. 1999, Wilcock et al. 2000). Other clinical data were collected using an informant-based semi-structured interview (Sano et al. 1995), disease onset and duration have been estimated using a set of questions developed by Doody and coauthors (2004) and the disease progression rate has been calculated with a formula using expected Mini-Mental State Examination (MMSE) scores, scores at presentation, and a standardized estimate of duration (Doody et al. 2001).

Treatment schedule, Aβ levels measurements, and determination of APOE genotype status

Rivastigmine has been prescribed at the initial dose of 3 mg/day (divided in two doses, morning and bedtime) after a meal. Dose escalation up to 12 mg per day in two divided doses was allowed throughout the study in at least 4-week intervals under condition of a good tolerance of the previously used dose. Dose reduction was allowed at any time point in case of poor tolerance of the previously prescribed dose.

A whole blood sample has been collected twice: before the first rivastigmine dose and at the second scheduled visit at week 2 of rivastigmine treatment. Methodological aspects of assessing the plasma levels of Aβ peptides have

Table I

Baseline demographic and clinical characteristics of the study population

Variable	Mean ± SD*	Range
Age (years)	77.6 ± 4.4	66–88
Gender (fraction of women)	0.69	N/A
Formal education (years)	7.2 ± 2.9	3–16
Age at onset	72.9 ± 4.1	65–80
Duration of the disease (years)	4.6 ± 2.5	1–13
Dementia severity:		
mild (CDR = 1)	0.46	N/A
moderate (CDR = 2)	0.54	N/A
Baseline MMSE (points)	17.7 ± 3.2	11–24
Baseline ADAS-cog (points)	32.7 ± 9.7	18–53
Rate of progression (points/year)**	3.4 ± 2.4	1.1–12

(*) except for gender and CDR measured dementia severity (fractions)

(**) calculated according to Sano and others (1995) as (30-MMSE) / estimated disease duration

Table II

Changes in mean plasma levels of Aβ after one-month treatment with a testing (3 mg/day) dose of rivastigmine

Plasma levels of Aβ (pg/ml)	At entry (before treatment)	After one month of rivastigmine treatment	Mean paired difference	*t*-test	*P*-value (2-tailed)
$Aβ_{1-40}$	171.5 ± 36.5	172.5 ± 32.9	1.0 ± 10.9	–0.6	0.5
$Aβ_{1-42}$	37.9 ± 11.6	44.0 ± 15.4	6.2 ± 6.9	–6.6	<0.001
$Aβ_{1-40}/Aβ_{1-42}$ ratio	4.8 ± 1.1	4.3 ± 1.4	0.5 ± 0.8	4.8	<0.001

been described in details elsewhere (Sobow and Kloszewska 2005, Sobow et al. 2005). In brief, a 10 ml blood sample was collected from fasting subjects in EDTA-containing recipients and the cellular material was pelleted by centrifugation. Plasma was stored at –4°C for a maximum of 4 hours and then frozen in 1 ml aliquots and stored at –70°C until the measurements. The concentrations of Aβ peptides ($Aβ_{1-40}$ and $Aβ_{1-42}$) in plasma were measured using a commercially available sandwich ELISA colorimetric assay (BioSource Intl, Inc) shown to be sensitive enough (range 15.6–1 000 pg/ml) to ensure an accurate result in plasma. Even though platelets have been regarded as a primary source of circulating βAPP and Aβ, no sampling technique modification preventing the activation of platelets was applied, based on data indicating the lack of any associations between platelet activation and plasma Aβ levels measured with a similar method (Olsson et al. 2003). Similarly, we did not introduce any additional procedures in cases of hypercholesterolemia treated with statins, as the very recent observations failed to observe a correlation between statins treatment and plasma Aβ levels while using the ELISA-based method (Hoglund et al. 2004).

Apolipoprotein E genotyping was performed in 44 subjects (supplementary informed consent was required; 10 subjects gave no consent or were not available for genotyping) using a PCR-RFLP method (Chapman et al. 1996).

Statistical analyses

Shapiro-Wilks W test was used as a formal test of normality and, additionally skewness and kurtosis between –2 to +2 were required to assume normality of distribution. Normalizing transformations were used if needed. A paired samples *t*-test was used to compare continuous variables (scores of psychometric scales and levels of Aβ) before and after treatment. A non-parametric Spearman's rho correlation was used as a measure of association (strength) of the relationship between two discrete variables. Multiple linear regression with backward stepwise method of entering variables into the model (stepping method criterion using probability of *F* with entry below 0.05 and removal at 0.1) was used to establish the predictive value of any baseline characteristics (including Aβ levels and psychometric tests scores) and Aβ levels change after rivastigmine treatment on the treatment effectiveness as measured by ADAS-cog score changes.

RESULTS

Baseline demographic characteristics of the study population (n=54) can be found in Table I. All subjects' data on plasma Aβ is available both at entry and after the initial dose of rivastigmine (3 mg/day) at one month. Paired samples *t*-test revealed that after one month of treatment with the initial (testing) dose of rivastigmine the mean plasma level of $Aβ_{1-42}$ increased significantly while no change in the plasma level of $Aβ_{1-40}$ has been observed; the calculated ratio $Aβ_{1-40}/Aβ_{1-42}$ decreased significantly as well (Table II). Fifty-one out of initially included 54 subjects finished the 6-month clinical observation being on rivastigmine treatment 6–12 mg/day. Three subjects (2 women) did not tolerate rivastigmine in the dose of at least 6mg/day and were excluded from further analyses. Mean values of either ADAS-cog or MMSE have not changed after 6 months, however, treatment response has been found to be variable. Fifteen patients (fraction 0.29) were classified as responders (at least a 3-point decline in the ADAS-Cog score), in 23 (fraction 0.45) no change was observed (scores between –2 to 2 from baseline) and 13 (fraction 0.26) did not respond to treatment (worsening of at least 3 points on the ADAS-cog scale). A comparison of responders to non-responders showed that those who improved had significantly higher initial ADAS-cog scores (and lower MMSE scores), shorter disease duration, faster rate of symptoms progression and a more pro-

Table III

Comparison of improvers *versus* decliners[†] on the ADAS-cog scale after 6 months of rivastigmine treatment

Variable[#]	ADAS-cog Improvers (n=15)	ADAS-cog Decliners (n=13)	Mean difference	P value* (2-tailed)
Initial ADAS-cog score	40.1 ± 7.5	27.1 ± 6.1	13.0 ± 2.6	<0.001
Initial MMSE score	16.1 ± 3.3	19.1 ± 2.3	3.0 ± 1.1	<0.01
Estimated disease duration (years)	3.1 ± 1.2	4.7 ± 1.8	1.6 ± 0.6	0.02
Calculated rate of symptoms progression (points of MMSE/year)	5.4 ± 2.9	2.7 ± 1.2	2.7 ± 0.8	<0.01
Change in plasma $A\beta_{1-42}$ level	12.0 ± 7.4	4.2 ± 4.8	7.8 ± 2.3	<0.01

([†]) improvers defined as those who improve 3 or more points on ADAS-cog, decliners – those who got worse 3 or more points; ([#]) only variables significantly different between the groups included in the Table; (*) Mann-Whitney U test

Table IV

Predictors of response to 6-month rivastigmine treatment[#] – best fit model summary*

Predictor	Standardized Coefficients	t-test	P value
Constant	–6.8		
Initial ADAS-cog score	0.33	2.8	<0.01
Calculated rate of progression	0.25	2.0	0.048
Plasma $A\beta_{1-42}$ level increase after one month of rivastigmine (3 mg/day) treatment	0.30	2.5	0.02

([#]) as measured by ADAS-cog score improvement resulting from multivariate linear regression analysis; (*) ANOVA, F-test 12.1, P<0.001; adjusted R square 0.39 with standard error of estimate 2.9, Durbin-Watson test 1.9

nounced increase in plasma $A\beta_{1-42}$ after one month of rivastigmine treatment (Table III). The improvement in ADAS-cog scores after 6 months of rivastigmine treatment correlated positively with a higher initial ADAS-cog score (r_s=0.48; P<0.001), faster disease progression estimated by a calculated rate of progression (r_s=0.46; P=0.002) and an increase in plasma $A\beta_{1-42}$ after one month of rivastigmine treatment (r_s=0.52; P=0.002); negative correlations were observed for the initial MMSE score (r_s= –0.37; P<0.1), estimated disease duration (r_s= –0.35; P=0.03) and a decrease in the calculated $A\beta_{1-40}/A\beta_{1-42}$ ratio at one month (r_s= –0.29; P=0.003). To confirm an association between the rate of progression and treatment response we have categorized all subjects who completed our study in two groups: fast progressors (those whose rate of progression was 3 points on MMSE a year or more) and slow progressors (rate of progression lower than 3 points per year). We found that the mean improvement of fast progressors (n=23) on the ADAS-Cog at month 6 of rivastigmine treatment was 2.2 ± 4.2 while slow progressors (n=28) actually got worse of mean 0.9 ± 2.8 (mean between-group difference 3.1 ± 1.0; independent samples t-test for equality of means after Levene's test for equality of variances (F=5.7; P=0.02), equal variances not assumed, t=3.1; P=0.004). Interestingly, no correlation between the level of improvement and the dose of rivastigmine used was observed. Considering apolipoprotein E genotype status (available for 44 subjects; 23 of them possessed at least one ε4 allele) we found no evidence of its influence on the level of improvement after 6 months of rivastigmine treatment. Subjects carrying at least one ApoE ε4 allele improved marginally better than those without this allele (mean difference 1.3 points on the ADAS-cog scale), this difference, however, did not reach statistical significance (Mann-Whitney U test, P=0.26). Multiple linear regression revealed that three variables may be considered best predictors of ADAS-cog change after 6 months of rivastigmine treatment: the initial ADAS-cog score, calculated disease progression and plasma $A\beta_{1-42}$ level change after one month of rivastigmine treatment. The higher the initial ADAS-cog, the faster the disease progression before treatment and the more pronounced the plasma $A\beta_{1-42}$ level increase after one month of rivastigmine treatment, the larger the improvement in ADAS-cog after 6 months of treatment (model summary in Table IV).

DISCUSSION

In dementia, and AD in particular, response to treatment is a poorly defined concept. Most of researchers, including us, refer to a pre-specified change in one of the commonly used evaluation scales (such as ADAS-cog, MMSE or Neuropsychiatric Inventory), bearing in mind mean changes observed in untreated subjects from historical cohorts as well as the results of pivotal randomized trials with ChEI. Using the abovementioned criterion the improvement on ADAS-cog of 3 points or more within a 6-month treatment period is considered "clinically meaningful" and a patient "a responder" or "an improver". Per analogy, a patient who got worse on this same scale of 3 points or more is considered "a non-responder" or "a decliner". In few studies a clinical rather than "scale-related" concept of response was applied, with an agreement between the researcher, the patient, and the caregiver demanded to claim the patient "a responder". Independently of response definition, not all AD patients improve during ChEI treatment. For example, a review of donepezil therapy indicated that the proportion of patients with AD showing a significant improvement in cognition was less than 40% (21%–38%) (Foster and Plosker 1999) while in another study behavioral response (as measured by NPI) to donepezil was seen in 41% of subjects (but 28% worsened) (Mega et al. 1999). Since ChEI treatment effects are highly variable and mean improvements reported in randomized controlled trials probably unrepresentative, predictors of response, understood as pre-treatment methods and characteristics which may help identify responders are highly desirable.

In our study several such predictors have been examined in a carefully selected cohort of 54 subjects. We have explored baseline demographic characteristics, disease severity (as measured by ADAS-cog and MMSE scores), its duration and age at onset (Doody et al. 2004), calculated disease progression rate (Doody et al. 2001) as well as apolipoprotein E genotype for their utility as potential predictors of treatment response. Additionally, plasma levels of amyloid β peptides (Aβ) and their changes after one month treatment with rivastigmine were for the very first time proposed as putative biochemical predictors of response after 6 months of rivastigmine use.

Considering baseline demographic characteristics we have not found any associations between them and treatment response as measured by change in ADAS-cog after 6 months. Lack of influence of age in our cohort is in conflict with findings relating younger age to better response in subjects treated both with donepezil (younger than 65) (Evans et al. 2000) and rivastigmine (younger than 75) (Bullock et al. 2006). We cannot, however, compare our results directly to those of Evans and coauthors (2000) since there were no subjects below the age of 65 in our study group. Once subjects were divided into two groups with a censoring age of 75, however, numerical (although not statistically significant) difference favoring younger subjects was seen (2.5 ± 3.6 *versus* 0.1 ± 3.7 change on ADAS-cog after 6 months; t=1.6, P=0.1). It is then possible that indeed patients younger than 75 years tend to respond better to rivastigmine than older ones, and the negative result in our cohort might be related to small sample size, particularly of younger subjects (n=8 only). Similarly to other reports we have not shown any correlations between age at onset or estimated disease duration and the extent of treatment response (Bullock et al. 2005, Evans et al. 2000). Higher initial ADAS-cog score (as a measure of symptomatic disease severity) claimed to be a strong predictor of response. In several other studies the same finding has been reported, indicating that moderately impaired subjects tend to respond better than mildly impaired (Bullock et al. 2005, Kaufer et al. 1998, Lilienfeld and Parys 2000, Schneider and Farlow 1996). Another strong predictor of response in our study was the rate of disease progression. This corresponds with the report of Farlow and colleagues (2001) who found that slowly progressive patients responded with a mean 1-point improvement while more rapidly progressive patients had a significantly larger mean of almost 5-point improvement at week 26. In our cohort fast progressors (calculated disease progression rate of 3 or more point-decline on MMSE per year) improved while slow progressors actually got worse. The finding that faster rate of symptomatic disease progression predicts better treatment response might in fact be associated with moderately impaired subjects tending to respond better than mildly ill patients, as it is well known that disease progression is not linear and significantly faster in moderate versus mild stages (Farlow et al. 2001, Schneider and Farlow 1996). Both predictors might also correspond with the fact that cholinergic dysfunction is more obvious in more

advanced stages of AD than in the initial phases of the disease (Davis et al. 1999) and thus more prone to pharmacological correction by ChEI. In line with this is the finding of a relative ineffectiveness of ChEI in mild cognitive impairment (Sobow and Kloszewska 2007).

The role of the ε4 allele of apolipoprotein E in predicting AD treatment response is controversial. Impaired response (Poirier et al. 1995), no effect (Aerssens et al. 2001 and the present study) and improved response (Lucotte et al. 1996) have all been associated with its presence. In a study by Poirier and others (1995) ApoE ε4 allele copy number showed an inverse relationship with residual brain ChAT activity and nicotinic receptor binding sites in both the hippocampal formation and the temporal cortex of AD subjects which might constitute a biological rationale of better treatment of subjects without ε4 allele.

Plasma Aβ levels have been proposed as a possible biomarker of AD, however, most of the studies in sporadic AD yielded, however, disappointing results (Flirski and Sobow 2005, Sobow et al. 2004), contrary to those in the familial forms of the disease or those examining the utility of plasma Aβ as a biomarker of mild cognitive impairment rather than AD itself (Sobow et al. 2005). In a recent study of our group we have found that the testing dose of rivastigmine (3 mg/day) taken for one month exhibited a significant effect on mean plasma concentrations of $A\beta_{1\text{-}42}$ (mean difference 7.8 ± 8.4, t= –4.9, P<0.001) with a negative correlation with the patients age (Pearson's R= –0.40, P=0.035) (Sobow and Kloszewska 2005). Here we confirmed this finding in a larger cohort of patients, however, correlation with age was no longer present. Moreover, the increase in $A\beta_{1\text{-}42}$ after the initial treatment with rivastigmine was shown to be a predictor of clinical response after 6 months. Since measuring plasma levels of $A\beta_{1\text{-}42}$ is technically feasible, should this finding be replicated, it might become an easy way in identifying ChEI responders. However, there are several possible limitations. First of all, it is not known whether our finding is drug-specific or not. It should be tested with other inhibitors (donepezil, galantamine), particularly in the context of a variable influence of ChEI on APP and amyloid metabolism (Lahiri et al. 2000). It would be particularly interesting to compare our finding with rivastigmine (which is a "dual" acetyl- and butyrylcholinesterase inhibitor) with other inhibitors, both selective (like donepezil) and dual (tacrine). Secondly, it is not clear whether our finding applies only to a 6-month period of treatment or might be generalized to longer periods as well. To address this issue, patients from our cohort are followed longitudinally. Lastly, since the levels of Aβ peptides measured in plasma vary significantly depending on the method of assessment, independent confirmations, using other kits (both commercially available and lab-prepared) are necessary before recommending it as a predictor of response. Our finding that a change in $A\beta_{1\text{-}42}$ plasma level after one month of an initial dose of rivastigmine may predict clinical response after 6 months represents a novel way of identifying patients with a good chance of response and might also contribute to a reduction of financial burden of public health care providers associated with ChEI use in "graying" westernized populations.

CONCLUSIONS

Looking for predictors of treatment response in AD is an important research task, particularly in the era of questioning drug effectiveness by regulatory bodies. Identifying subjects who may respond better is also important to patients themselves as well as their caregivers. Here, we have shown that a relatively simple blood (plasma Aβ level assessed by a commercially available ELISA) test done twice (before treatment and after one month of drug testing dose) might be useful in predicting response in a case of rivastigmine. Moreover, we confirmed that there are some individual and easy-to-asses patients' characteristics, namely dementia severity and its progression rate, that may also help in distinguishing those who have better chance of responding within 6 month of treatment. More research is needed to prove whether these findings are also valid in the longer treatment durations and with the use of other than rivastigmine cholinesterase inhibitors or memantine.

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