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Featured Article

Alzheimer's disease progression model using disability assessment for dementia scores from bapineuzumab trials

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Abstract

Objective: Disability assessment for dementia (DAD) measurements from two phase-3 studies of bapineuzumab in *APOE* ε4 noncarrier and carrier Alzheimer's disease (AD) patients were integrated to develop a disease progression model.

Methods: We evaluated longitudinal changes in DAD scores, baseline factors affecting disease progression, and bapineuzumab effect on disease progression.

Results: A beta regression model best described DAD disease progression. The estimated treatment effect of bapineuzumab was not significant, consistent with lack of clinical efficacy observed in the primary analysis. The model suggested that progression of DAD tended to decrease with increase in bapineuzumab exposure. The exposure-response relationship was similar regardless of *APOE* ε4 status but more pronounced in patients with mild AD. Baseline disease status, age, memantine use, and years since onset (YSO) had significant effects on baseline DAD scores. AD concomitant medication use, baseline disease status, and YSO had significant effects on disease progression rate, measured by DAD score.

Conclusions: The beta regression model is a sensible modeling approach to characterize functional decline in AD patients. This analysis suggested a possible effect of bapineuzumab exposure on DAD progression. Further evaluation may be warranted in future studies.

Trial Registration: ClinicalTrials.gov identifier: NCT00575055 and NCT00574132.

Keywords: Disability assessment for dementia; Bapineuzumab; Alzheimer's disease; Disease progression model

1. Introduction

Alzheimer's disease (AD) progression varies among different individuals, advancing from normal to prodromal predementia, mild cognitive impairment, and dementia [1]. Currently available AD treatments mainly provide temporary enhancement of impaired neurotransmitter systems to maximize remaining activity in disease-affected neuronal populations [2–4]. They do not address underlying disease process or progression of cognitive and functional decline. With a goal of expanding treatment options for AD population, development of new disease-modifying

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therapeutics, designed to alter the underlying pathophysiology and change the course of AD, are underway.

Population disease progression modeling is an efficient way to comprehensively integrate and use available information. Simulation models applied to normal individuals, and those with mild cognitive impairment or AD, are a key step in the early detection and tracking of AD. In this context, disease progression models focusing on cognitive deterioration, as measured by a longitudinal response using the AD assessment scale-cognitive subscale (ADAS-cog), are well-accepted [5–9]. However, models characterizing functional decline in AD are not available to date.

Disability assessment for dementia (DAD) scale is an important and convenient tool to assess functional impairment, a core symptom of AD often measured by loss of ability to perform activities of daily living. The DAD scale is easy and quick to administer, taking <15 minutes without any requirement of a particular setting nor does it require any special equipment. Another advantage of this scale is that it does not require any particular expertise or extensive training for administration. A user guide is available to ensure proper administration and scoring of the instrument [10]. In two phase-3 studies, bapineuzumab, an anti-amyloid β monoclonal antibody, was investigated for its therapeutic effect on cognitive and functional decline in mild-to-moderate AD [11]. However, efficacy was not demonstrated in either study. The goal of the current analysis was to model the disease progression, as measured by DAD scores, using combined data from the two bapineuzumab phase-3 studies to allow for a better understanding of the changes in DAD scores during disease progression, baseline factors affecting progression of DAD scores, and the relationship between bapineuzumab exposure and DAD score progression.

2. Methods

2.1. Clinical data

The data set used in this disease progression analysis comprised pooled data from two phase-3 studies of bapineuzumab in patients with mild-to-moderate AD who were either apolipoprotein E, E4 allele (*APOE* ε4) noncarriers (study 301, NCT00574132) or carriers (study 302, NCT00575055). Details of the inclusion/exclusion criteria and primary results of the two studies are available in the literature [11]. The DAD score was the primary functional outcome measure for assessing clinical efficacy in studies 301 and 302, and DAD assessments were performed at prescheduled time points i.e. weeks 0, 13, 26, 39, 52, 65, and 78. The data set for this analysis included all DAD measurements from both studies with an available date and time of testing.

2.2. Model development

Disease progression models were established using NONMEM (version 7.1.0 with a GNU FORTRAN compiler; Icon Development Solutions, Ellicott city, MD, USA). Data exploration and visualization were performed using R (http://www.r-project.org; version 2.14.0) and Xpose package 4.0 (http://xpose.sourceforge.net).

2.2.1. Structural model

A mixed-effect beta regression model was selected after testing 10 basic models available in the literature [5,7,12–14]. The model selection criteria were (1) Akaike information criterion; (2) goodness-of-fit diagnostics; and (3) ill conditioning and overparameterization by inspecting the eigenvalues of the covariance matrix (ratio of the largest eigenvalue to the smallest eigenvalue to be <1000).

The beta regression model assumed that DAD scores follow a beta distribution as denoted by

$$y_{ij}\left|\eta_i, \theta, \tau \sim beta\left(\mu_{ij}\tau, \left(1-\mu_{ij}\right)\tau\right)\right.$$

where y_{ij} is the response variable ($0 \le y_{ij} \le 1$, i.e., DAD/100) for the i^{th} patient ($i = 1\ldots m$) at the j^{th} time ($j = 1\ldots n_j$), μ_{ij} is the conditional expectation (mean) of the response process ($0< \mu_{ij} <1$), η_i's are the random effects following a multivariate normal distribution ($\eta_i \sim N[0, \Sigma]$, θ's are the fixed effects (parameter coefficients), and τ is the precision parameter ($\tau > 0$). The expected mean response model for DAD followed a linear progression model (on the logit scale) with an intercept (θ_0) and slope on time (θ_1):

$$\log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = \theta_0 + \eta_{0i} + (\theta_1 + \eta_{1i}) \bullet t_{ij} \qquad (1)$$

The beta regression model requires data residing within the range of 0–100 [15,16], and therefore y_{ij} were rescaled by a small noise factor ($\delta = 0.01$) to move the boundary observations slightly away from the edges [16,17].

2.2.2. Placebo model

The placebo effect (defined as transient improvement in function during the initial period of weeks to months after the treatment) has not been characterized for DAD score progression in any past studies to date. The choice of structural form of the placebo function was driven by prior knowledge [5,18,19]. Inverse Bateman function (IBF) and exponential functions were explored to test the presence of the placebo effect for DAD scores.

2.2.3. Covariate model

To date, covariates affecting progression of DAD scores remain unknown because of the knowledge gap in the published literature. Previously known ADAS-Cog score models [6,7] have identified age, *APOE* ε4 carrier status, AD concomitant medications (cholinesterase inhibitors or/and memantine), sex, and years since disease onset (YSO) as potential factors influencing disease progression. Thus, we preselected these covariates to be tested on both intercept and slope of the beta regression model for the DAD scores (Eq. 1).

A full covariate model was constructed and backward elimination was performed to identify a parsimonious covariate model [20]. Effects of covariates were considered significant if the increase in objective function value (OFV) value was >7.88 ($P < .005$) on its removal to avoid inclusion of insignificant covariates into the model due to multiple comparisons.

2.2.4. Drug model: Bapineuzumab effect

The bapineuzumab effect on disease progression was investigated at two different levels: treatment level to evaluate the treatment effect versus the placebo and individual level to evaluate the exposure-response relationship using individual pharmacokinetic or concentration data (e.g. area under the serum concentration-time curve [AUC] or trough serum concentration [C_{trough}]) based on a population pharmacokinetic model for bapineuzumab [21]. An exploratory graphical analysis was first performed followed by a formal model evaluation. The interaction between the drug effect and other covariates (baseline disease status and *APOE* ε4 carrier status) was also tested.

Three sensitivity analyses were performed to further investigate the exposure-response relationship. Because the primary clinical analysis was performed in the modified intention-to-treat population (mITT, i.e. all randomized patients who received at least one infusion or portion of an infusion of study drug and who had a baseline and at least one postbaseline assessment of the ADAS-Cog/11 total score and DAD total score) but the beta regression model was developed using the overall population, the first sensitivity analysis was conducted to confirm the exposure-response relationship in the primary analysis data set. In addition, the DAD scores appear improved in the bapineuzumab group at weeks 65 and 78 (Fig. 1) in study 301. However, such improvement was not observed for the concurrently measured coprimary end point (ADAS-cog scores), so it could have been a spurious effect due to variability. Therefore, two more sensitivity analyses were performed to assess the impact of the improvements in DAD scores at the end of weeks 65 and 78 in study 301 on the exposure-response relationship after excluding these data from the analysis (i.e. after excluding only week 78 data for patients in bapineuzumab group in study 301 and after excluding both weeks 65 and 78 data for patients in bapineuzumab group in study 301).

2.3. Missing data

An analysis to explore the mechanism for missing data was performed. A grouped-time survival model was used to model missing data [22,23].

Complementary log-log (clog-log) link function was used because it yields a grouped-time proportional hazards model, and this can be advantageous for interpreting model parameters compared with other link functions (e.g. logit).

2.4. Model evaluation

The beta regression model was evaluated using percentile visual predictive check (VPC), where the level to which the median prediction or/and extremes of 90% prediction interval replicated the median, 5th, and 95th percentiles of the observed data at respective time points (weeks 0, 13, 26, 39, 52, 65, and 78), was evaluated with confidence intervals [24]. To facilitate the comparison of the observed data to the simulated data in the VPC analysis, the missing data event was simulated based on the conditional probability at each time point, assuming a binomial distribution for the missing event.

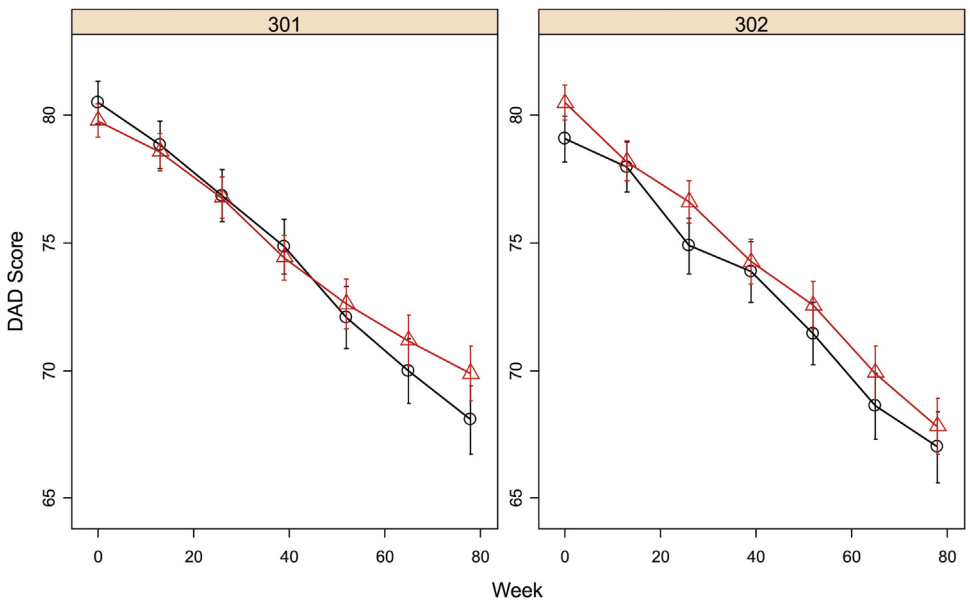

Fig. 1. Exploratory analysis for bapineuzumab treatment effect for studies 301 and 302: observed average (mean) DAD scores versus time. Bapineuzumab was administered as 0.5 or 1.0 mg/kg infused intravenously for 1 hour/13 weeks for six infusions in *APOE* ε4 noncarrier (study 301) or carrier (study 302) patients with mild-to-moderate AD; vertical error bar represents the standard deviation of the mean DAD scores. Abbreviation: DAD, disability assessment for dementia.

Table 1
Bapineuzumab steady-state exposure metrics considered in the exposure response analyses

Bapineuzumab dose level	n	Mean ± standard deviation	
		C_{trough} (μg/mL)	AUC (μg d/mL)
Study 301—0.5 mg/kg	337	0.64 ± 0.3	211.8 ± 53
Study 301—1 mg/kg	329	1.26 ± 0.6	412.6 ± 94
Study 301—2 mg/kg*	141	1.77 ± 0.9	608.5 ± 161
Study 302—0.5 mg/kg	673	0.65 ± 0.3	211.4 ± 50

Abbreviations: C_{trough}, trough serum concentration; AUC, area under the serum concentration-time curve.

*Initially, there was also a 2.0-mg/kg dose level in study 301, but this dose level was discontinued as of protocol amendment 1. Patients who had already been randomly assigned to bapineuzumab 2.0 mg/kg were treated with 1.0 mg/kg for the remainder of the study. None of the patients completed the study at the 2.0-mg/kg dose level.

3. Results

This analysis included data from 2452 patients from studies 301 and 302, in which 972 patients were treated with placebo and 1480 with bapineuzumab, and all patients had at least 1 DAD measurement. Further details on patient characteristics are described elsewhere [11]. Briefly, 46% were men and 54% were women. The mean age ± standard deviation was 72.6 ± 9.0 years, and patients had AD for a mean duration of 3.2 ± 2.4 years. The mean baseline mini mental state examination (MMSE) and DAD scores were 21 ± 3.2 and 80 ± 19, respectively. Based on mild versus moderate AD definitions of baseline MMSE score ≥21 versus ≤20, respectively, 54% of patients had mild AD and 46% had moderate AD. A total of 11.3% patients were homozygous for the *APOE* ε4 allele, 33.5% were *APOE* ε4 heterozygous, and 54.2% were *APOE* ε4 noncarriers. A total of 90.5% patients took AD concomitant medications, i.e. 53% took acetylcholinesterase inhibitors and memantine; 33% took acetylcholinesterase inhibitors alone; and 4.4% took memantine alone.

In the two studies combined, 40% of all patients were randomized to placebo, 41% were randomized to bapineuzumab 0.5 mg/kg, 13% were randomized to bapineuzumab 1 mg/kg, and 6% were originally randomized to bapineuzumab 2 mg/kg. After a protocol amendment in April 2009, the 2 mg/kg dose in study 301 was reduced to 1 mg/kg. The steady-state exposure to bapineuzumab (AUC and C_{trough}) over the duration of the studies is summarized by bapineuzumab dose level in Table 1. The drug exposure is nearly identical at 0.5 mg/kg in the *APOE* ε4 noncarriers (study 301) and carriers (study 302). The exposure proportionally increased when dose increased from 0.5 to 1 mg/kg. The exposure in patients randomized to 2 mg/kg was approximately 40% higher than that in patients on 1 mg/kg.

3.1. Population mean estimates of baseline and disease progression according to DAD

The parameter estimates of the final model are summarized in Table 2. The population mean of baseline DAD score in a typical 74-year-old patient with mild AD (no

Table 2
Parameter estimates of the beta regression model

Parameter estimates	Logit scale			Original scale		
	Estimate	95% confidence interval		Estimate	95% confidence interval	
Baseline						
Mild AD	2.23	2.14	2.32	90.29	89.49	91.04
Moderate AD	1.39	1.29	1.49	80.06	78.48	81.55
Covariates on baseline						
Sex (men)	0.061	−0.03	0.15	1.52	−0.67	3.70
Use of memantine	−0.318	−0.41	−0.23	−7.95	−10.22	−5.68
Age (y)	−0.020	−0.02	−0.01	−0.49	−0.61	−0.37
YSO (y)	−0.047	−0.07	−0.03	−1.17	−1.66	−0.68
Progression rate (points/y)	−0.006	−0.009	−0.003	−7.58	−11.25	−3.91
Covariates on progression rate						
MMSE	0.0013	0.0010	0.0016	1.70	1.34	2.06
Use of memantine or cholinesterase inhibitors	−0.0072	−0.0100	−0.0044	−9.39	−13.00	−5.77
YSO (y)	0.0006	0.0003	0.0008	0.76	0.41	1.10
Exposure-response on progression rate						
Mild AD, AUC (1000 μg d/mL)	0.0059	0.0011	0.0107	7.72	1.48	13.96
Moderate AD, AUC (1000 μg d/mL)	0.0026	−0.0022	0.0073	3.32	−2.88	9.51
SD of IIV on intercept	1.09	1.02	1.16	27.25	25.40	29.10
SD of IIV on slope	0.0002	0.0001	0.0002	0.226	0.183	0.269
Precision parameter	3.19	3.14	3.24	—	—	—

Abbreviations: AD, Alzheimer's disease; YSO, years since onset of Alzheimer's disease; MMSE, mini mental state examination; AUC, area under the serum concentration-time curve; SD, standard deviation; IIV, Interindividual variability; DAD, disability assessment for dementia.

NOTE. The parameter estimates for the beta regression model do not have a direct interpretation on the original scale because of the logit transformation used in the model. Therefore, to facilitate interpretation, the marginal effect of covariates and rate of progression were evaluated at a DAD score of 50.

memantine use, YSO = 2.83 years) was 90, whereas it was 80 for a patient with moderate AD. The progression rate for a typical placebo patient with baseline MMSE score of 21, YSO of 2.83 years, who did not take memantine or acetylcholinesterase inhibitor (approximately 9.5% of the overall patients) was −7.6 points/year.

3.2. Covariate effects on disease progression parameters

Analysis of baseline covariates demonstrated that memantine use, age, YSO, and baseline disease status (i.e. mild or moderate AD) had statistically significant effects on baseline DAD scores ($P \leq .0005$), whereas use of AD concomitant medications (i.e. memantine or acetylcholinesterase inhibitors), baseline disease status, and YSO had statistically significant effects on the rate of disease progression as measured by DAD scores ($P < .0001$). *APOE* ε4 carrier status (homozygous vs. heterozygous or carrier vs. non-carrier) had no significant effect on either the baseline DAD score or the disease progression rate.

The baseline DAD score for patients taking memantine at baseline was approximately 8.0 (95% confidence interval [CI], 5.7–10.2) points lower than those not taking memantine. The baseline DAD score decreased for each additional year of having the disease by 0.5 (95% CI, 0.4–0.6) points and 1.2 (95% CI, 0.7–1.7) points for older age and YSO at baseline, respectively. The effect of sex was not significant on baseline DAD score ($P > .05$).

Patients who had used AD concomitant medications at baseline tended to have greater disease progression rate. The progression rate of the DAD score was 17 points per year for patients who were in the placebo arm and taking memantine or acetylcholinesterase inhibitors (∼90.5% of study patients), as compared with 7.6 (95% CI, 3.9–11.5) points/year for those not taking these AD concomitant medications. It was reported that average decline in DAD was approximately 15 points after a year for patients with mild-to-moderate AD dementia [25]. The mean change in DAD score after a year appeared to be approximately 10–12 points in a phase-2 bapineuzumab study [26]. Our result for patients is consistent with the published values. Patients with less disease severity at baseline had slower rates of disease progression. For every unit of increase in MMSE score, the DAD score progression rate decreased by approximately 1.7 (95% CI, 1.3–2.1) points/year. In addition, patients with higher YSO at baseline had slower DAD score progression rates (0.8 points/year/YSO [95% CI, 0.4–1.1]).

3.3. Placebo model

Placebo models with three-parameter IBF function or two-parameter exponential function were tested, but neither of them significantly improved the DAD disease progression model. Both placebo models led to a decrease of 4 points in OFV for the disease progression model ($P = .26$ for three-parameter IBF model and $P = .14$ for two-parameter exponential model), suggesting that a placebo effect (defined as transient improvement in function) was minimal in both studies. However, the placebo effect might not be well-estimated in this model due to the sparse data.

3.4. Bapineuzumab effect

3.4.1. Treatment effect

Disease progression profiles appeared to be similar for bapineuzumab and placebo groups (Fig. 1). However, the bapineuzumab group tended to have a slower DAD score progression rate after week 52. There was no apparent difference in the trend for *APOE* ε4 carriers and noncarriers. After adding treatment information to the beta regression model, OFV of the model improved by 2.7 points ($P = .1$), indicating treatment effect was not a significant factor affecting DAD disease progression. This observation is consistent with the lack of efficacy observed in the studies, albeit the estimated effect was directionally consistent with the hypothesized drug effect.

3.4.2. Exposure-response relationship of bapineuzumab

Fig. 2 indicates that the exposure-response relationship was apparent in patients with mild AD in study 301 (*APOE* ε4 non-carriers), and with increase in drug exposure, DAD progression rate slowed. In both bapineuzumab exposed groups, separation of disease progression profiles was observed after week 39 versus placebo group. Such a trend was less apparent in study 302 (*APOE* ε4 carriers) because it tested only the low dose and in moderate AD patients from study 301 (*APOE* ε4 noncarriers).

The beta regression model revealed a marginal but positive association between bapineuzumab exposure (i.e., AUC) and slowing of disease progression rate. The DAD score progression rate decreased by 7.7 (95% CI, 1.5–14) points/year and 3.3 (95% CI, −2.9 to 9.5) points/year for every 1000-μg d/mL AUC increase in patients with mild AD and moderate AD, respectively (Table 2). The estimated reduction in progression rate would be 3.2 points/year and 1.4 points/year at 1 mg/kg (AUC = 412.6 μg d/mL) for patients with mild and moderate AD, respectively. The analysis suggested that the exposure-response relationship was similar regardless of *APOE* ε4 carrier status (carrier or noncarrier) as the interaction between *APOE* ε4 carrier status and bapineuzumab exposure was not significant ($P = .29$).

In the first sensitivity analysis, the estimated exposure-response in mild AD patients was only 3% higher in the mITT population than in the overall population (Table 3), suggesting that the model parameter estimation was not sensitive to the exclusion of patients for the mITT population. After exclusion of week 78 data, the exposure-response relationship in patients with mild AD was reduced slightly by 5.9%. In contrast, after excluding the data from weeks 65 and 78, the exposure-response relationship

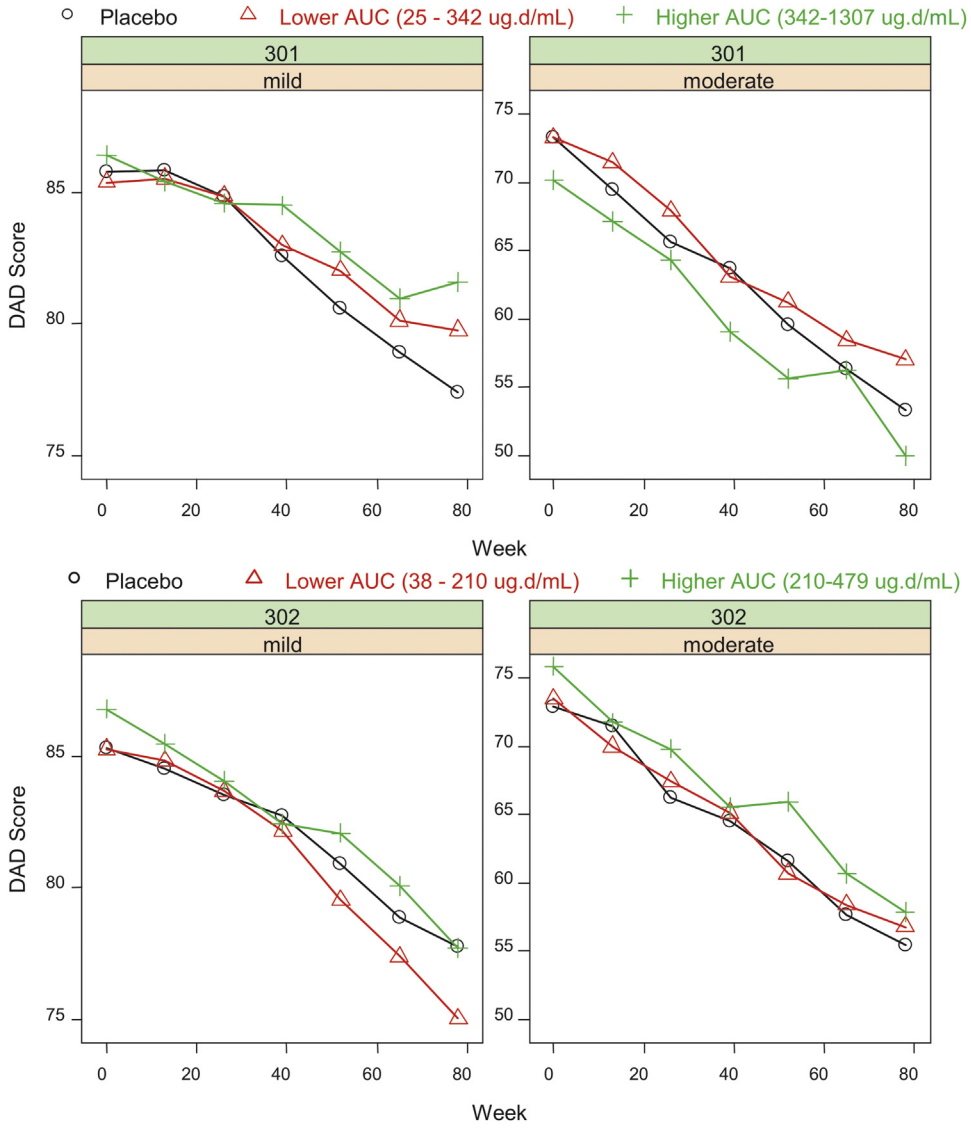

Fig. 2. Exposure-response relationship for bapineuzumab by study and severity of Alzheimer's disease: Observed average (mean) DAD scores versus time. Steady-state AUC is used. Patients treated with bapineuzumab were grouped by median AUC for each study. Abbreviations: DAD, disability assessment for dementia; AUC, area under the serum concentration-time curve.

increased by 22.4%. Both sensitivity analyses indicated that the possible effect of bapineuzumab exposure on slowing DAD progression in patients with mild AD was not caused by the improvement in DAD scores at the end of study. This is not unexpected because this trend was apparent as early as in week 39 in patients with mild AD in study 301 (Fig. 2).

3.5. Missing data analysis

The probability of missingness was significantly ($P < .0001$) dependent on DAD score before the event and patient's baseline age. The hazards of missing decreased by 2% for every unit increase in DAD score before the event, whereas it increased by 2.4% for every year of increase in age. This finding confirmed that "missing completely at random" was not the missing data mechanism and that missing at random may be a more reasonable assumption, which was consistent with the assumption for the primary statistical analysis (mixed-effect model with repeated measure).

3.6. Model evaluation

The VPC suggested that the disease progression model not only described the overall longitudinal progression of the DAD scores well (Fig. 3A) but also adequately described the exposure-response relationship between bapineuzumab exposure and longitudinal DAD score progression (Fig. 3B). Additional VPC plots for patients with mild and moderate AD are provided in Supplementary Figs. 1 and 2, respectively.

Table 3
Parameter estimates of exposure-response for bapineuzumab from the sensitivity analyses

Data set	Exposure-response on logit scale			% change versus reference	0 within 95% CI
	Estimate	95% CI			
Mild AD					
Overall population	0.0059	0.0011	0.0107	Reference	No
mITT population	0.0061	0.0013	0.0109	3.0	No
Week 78*	0.0056	0.0004	0.0108	−5.9	No
Weeks 65 and 78†	0.0073	0.0016	0.0129	22.4	No
Moderate AD					
Overall population	0.0026	−0.0022	0.0073	Reference	Yes
mITT population	0.0021	−0.0027	0.0068	−19.2	Yes
Week 78*	0.0039	−0.0010	0.0089	54.5	Yes
Weeks 65 and 78†	0.0034	−0.0019	0.0086	31.4	Yes

Abbreviations: CI, confidence interval; AD, Alzheimer's disease; mITT, modified intention-to-treat.
*Week 78 = population after excluding all week 78 data for patients in bapineuzumab group in study 301.
†Weeks 65 and 78 = population after excluding all week 65 and 78 data for patients in the bapineuzumab group in study 301.

4. Discussion

This modeling approach attempts to provide a novel methodological framework to describe and interpret AD progression in terms of DAD scores and of the effects of covariates on disease progression. The impact of covariates on the progression of DAD scores has not yet been characterized in the literature for disease progression models, and thus remains unknown. Our analysis addresses this gap by identifying the covariates (demographics and baseline characteristics) contributing to the variability in disease progression rate and baseline disease status among mild-to-moderate AD patients. However, as this is the first attempt to model the longitudinal progression of DAD scores, previously identified covariates on cognitive tests (e.g. ADAS-cog score) were evaluated. Similar approach has been used when modeling other AD functional measures [27]. Because of the potential difference between the functional and cognitive progression of the AD, other covariates that were not included in the current analysis may also affect the function in AD patients.

Beta regression models were recently qualified as a quantitative clinical trial simulation tool for ADAS-cog/11 by the

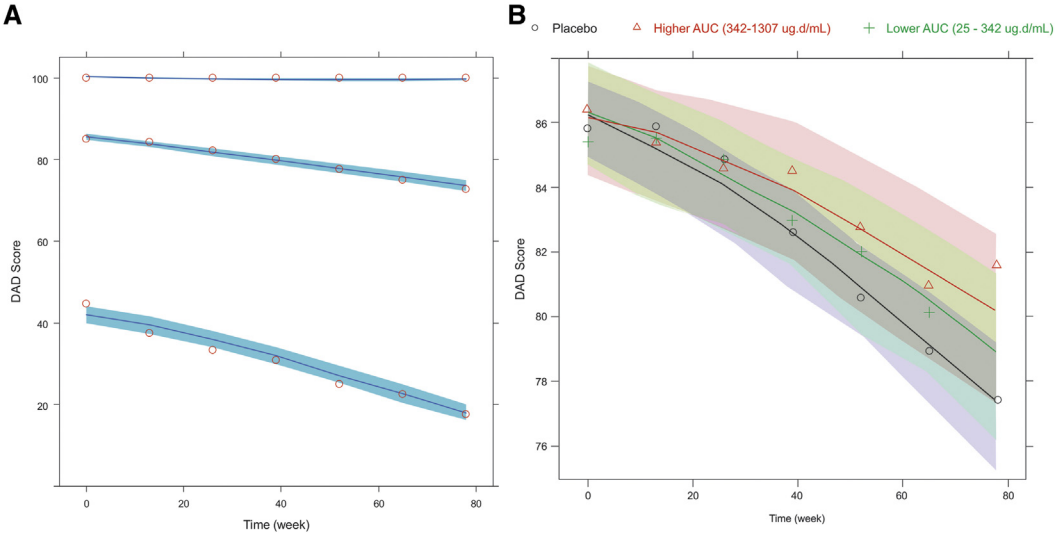

Fig. 3. (A). Visual predictive check for the beta regression model based on the overall data from studies 301 and 302. The upper, middle, and lower profiles indicated by the open circles represent the 95th, 50th, and 5th percentiles of the observed data, respectively. The upper, middle, and lower curves indicated by the lines are the median model-based prediction for the 95th, 50th, and 5th percentiles, respectively, and these predictions account for missing data. The shaded areas are the 90% confidence intervals of the corresponding percentiles of the simulations based on the model. The beta regression model listed in Table 2 was used for the simulations. (B). Stratified visual predictive check for patients with mild Alzheimer's disease in study 301: exposure-response relationship. The symbols represent the mean of the observed data. The curves indicated by the lines are the mean model-based predictions that account for missing data. The shaded areas are the 90% confidence intervals of the corresponding predictions based on the model. The beta regression model listed in Table 2 was used for the simulations. Abbreviations: DAD, disability assessment for dementia; AUC, area under the serum concentration-time curve [11].

Food and Drugs Administration and European Medicines Agency for mild-to-moderate AD [28,29]. The current analysis suggested that beta regression models are also sensible modeling choice for DAD scores. Similar to ADAS-cog scores, DAD scores also represent a bounded outcome. Beta regression models have been shown to well describe and predict the bounded outcome data with nonlinear mean and the heteroscedastic variance due to the ceiling/floor effects [30,31].

Because AD patients may be able to learn aspects of cognition tests such as ADAS-cog test, and complicated implementation of cognition tests may cause rater's bias, transient placebo improvement has often been found on cognitive end points. A placebo effect was not observed in the current analysis on the functional DAD test. This may be suggestive that functional tests may be less susceptible to the learning effects and rater's bias. Therefore, modeling functional AD measures such as DAD score could provide additional useful information that could not be obtained from ADAS-Cog disease progression models.

The analyses based on either the treatment groups or the individual bapineuzumab exposure levels demonstrated a trend of improvement of function in mild AD patients after the treatment with bapineuzumab. The trend was not found to be statistically significant among treatment groups, whereas the individual exposure-response relationship appeared to be marginally significant. This is probably because individual exposure levels could provide richer information regarding the drug exposure than the dichotomous treatment groups. According to the sensitivity analyses, the exposure-response trend was not attributable to the increase in the DAD scores after week 65. In patients with moderate AD, the directionality of the estimated bapineuzumab effect was consistent with that for the mild AD patients, but the magnitude of the estimated bapineuzumab effect was less pronounced compared with that in mild AD.

5. Conclusion

A beta regression logistic model best described disease progression as measured by DAD scores for patients with mild-to-moderate AD in studies 301 and 302. The model suggested a possible effect of bapineuzumab exposure on DAD progression, i.e. disease progression according to the DAD score decreased with increased bapineuzumab exposure. The exposure-response relationship was similar regardless of *APOE* ε4 status but more pronounced in patients with mild AD. Baseline disease status, age, memantine use, and disease duration had significant effects on baseline DAD scores. Use of AD concomitant medications, baseline disease status (mild AD vs. moderate AD), and disease duration had significant effects on DAD score disease progression rate. The relation to AD comedication use is likely due to patients with faster progression rates being more likely to receive treatment for AD.

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All authors contributed in the design of the analysis plan and interpretation of the data. M.N.S. and S.X.X. contributed equally in the analysis of the data.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2015.06.005.

RESEARCH IN CONTEXT

1. Systemic review: The authors developed a disease progression model based on pooled disability assessment for dementia (DAD) score data from two phase-3 studies of bapineuzumab in patients with mild-to-moderate Alzheimer's Disease (AD) who were either *APOE* ε4 noncarriers or carriers.
2. Interpretation: The model suggested a possible effect of bapineuzumab exposure on DAD progression, i.e. disease progression according to the DAD score decreased with increased bapineuzumab exposure. The exposure-response relationship was similar regardless of *APOE* ε4 status but more pronounced in patients with mild AD. Baseline disease status, age, memantine use, and disease duration had significant effects on baseline DAD scores. Use of AD concomitant medications, baseline disease status (mild AD vs. moderate AD), and disease duration had significant effects on DAD score disease progression rate.
3. Future directions: This modeling approach provides a novel methodological framework to describe and interpret AD progression in terms of DAD scores and of the effects of covariates on disease progression, which could assist in the design of future clinical studies.

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