Assessing the Cumulative Exposure Response in Alzheimer Disease Studies

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Abstract

BACKGROUND: To assess long-term cumulative benefit of a treatment and to answer questions such as "how high" or "how long" the treatment needs to be, the relationship between cumulative drug exposure and outcomes could be explored to understand dose response. Cumulative exposure corresponds to the longitudinal profile of an outcome, which is heavily confounded with natural disease progression and missing data, especially in trials of neurodegenerative diseases (eg, Alzheimer's disease) due to long duration follow-ups. These confounding factors may need to be adjusted when assessing the exposure response.
METHODS: A model-based approach is developed to account for the confounding factors: first, a disease progression model is constructed to represent the natural disease progression over the time course of the trial, where subject-level characteristics and dropout timing are taken into consideration; then, the observed outcome measures are adjusted by the projected disease progression at the corresponding timepoints; finally, the resulting model-adjusted outcome measures are linked with the level of cumulative exposure (AUC).
RESULTS: The proposed approach introduces important new insights to the interpretation of study data. In particular, in the case study used to demonstrate the method, there seem to be various degrees of efficacy trend favoring higher level of cumulative exposure in active drug, based on selected clinical and biomarker endpoints.

Background

Typical questions being asked during drug development include "how high" the dose or "how long" the treatment duration needs to be. These questions are naturally answered by assessing the relationship between cumulative drug exposure and cumulative treatment effect. However, in clinical trials, understanding the real cumulative treatment effect is often difficult as the observed outcome measure is a mixture of multiple factors:

- **drug effect**: the actual treatment difference over placebo
- **natural disease progression**: the deterioration observed under naïve treatment
- **missing data impact**: eg, early dropouts may have shown greater deterioration

This complexity is particularly clear for a clinical trial with long follow-up period such as a neurodegenerative disease (eg, Alzheimer's disease).

Consider a clinical study where the cumulative drug exposure (AUC) and the last observed response (change from baseline) is illustrated in Figure-1. Several points to note:

- placebo (AUC=0) arm: score increased → natural progression (understandable)
- active arms (AUC>0): upward trend:
  - higher cumulative AUC → greater disease progression (????)
  - early dropouts: lower cumulative AUC, shorter time for disease progression

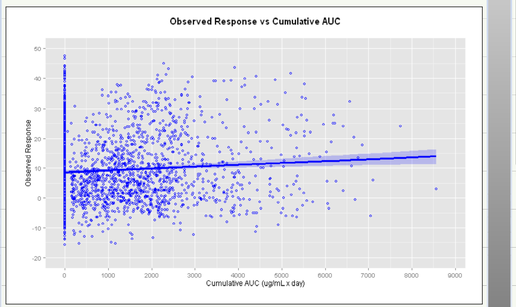


Figure-1. Scatter plot of observed response vs. cumulative AUC.

Intuitively…

Need a method to

- estimate the pure drug effect
  - model the disease progression: so we know the drug benefit over placebo
  - control the "time component": so the observed responses are comparable
- connect the pure drug effect with the cumulative drug exposure
- WORK & MAKE SENSE!

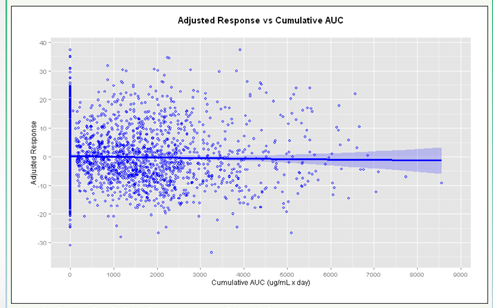


Figure-2. Scatter plot of adjusted response vs. cumulative AUC.

If we knew the disease progression…

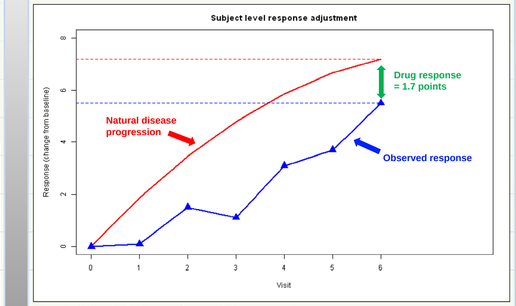


Figure-3. Subject level adjustment for natural disease progression.

Observed response = natural disease progression + drug response

↓

Drug response = benefit over placebo (drug effect)

↓

Est. drug effect = observed response – est. disease progression

Method

Step 1: A disease progression model

- Any disease progression model can be tested
  - characterizes the longitudinal profile of the progression
  - differentiates patients with distinct disease severity
  - recognizes dropout effect
- Subject-level projection of disease progression
  - subjects with different baseline condition → different progression path
  - subjects with identical baseline condition but different dropout time → different progression path
- Eg, a mixed-effect model with repeated measures (MMRM)
  - data at multiple timepoints
  - considers subject-level (eg, demographics) information
  - considers time to dropout

Step 2: Adjusted observations

- Collect the last available measurement
- Calculate the projected disease progression at the corresponding time point
- Subtract the projected disease progression from the observed value
- Do this for EVERYONE

Step 3: Exposure response

- Connects cumulative exposure (AUC) with adjusted response
- Linear regression?

$$Response_{adj} = \alpha + \beta \cdot AUC_{cum}$$

- Emax?

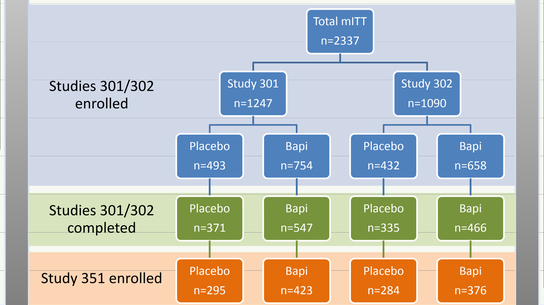
$$Response_{adj} = \alpha + \frac{\beta \cdot AUC_{cum}}{\gamma + AUC_{cum}}$$

- LOESS? Fancier?

A Case Study

Bapineuzumab IV was studied at multiple doses in mild to moderate Alzheimer's disease patients. Three phase 3 studies were conducted mainly in North America:

- Study Protocol ELN115727-301 (Study 301): Apolipoprotein E ε4 carriers
- Study Protocol ELN115727-302 (Study 302): Apolipoprotein E ε4 noncarriers
- Study Protocol ELN115727-351 (Study 351): open-label extension of Studies 301/302



Disease progression model

- Constructed separately for Study 301/302/351
- Used placebo data only (with modification for Study 351)
- Based on an MMRM with
  - visit schedule
  - baseline age
  - randomization strata
  - baseline value of the corresponding variable
  - time to dropout
  - baseline value * visit interaction

Noncarrier		Carrier	
Model Terms	**Coefficient Estimate (SE)**	**Model Terms**	**Coefficient Estimate (SE)**
Intercept	5.6499 (2.2179)	Intercept	7.8834 (2.6256)
Baseline	0.2271 (0.04810)	Baseline	0.2300 (0.05580)
Age	-0.04427 (0.02163)	Age	-0.04704 (0.02734)
Time to dropout/complete	-0.01961 (0.01168)	Time to dropout/complete	-0.02646 (0.01252)
MMSE | Low	2.8437 (0.5386)	MMSE | Low	1.9702 (0.5427)
MMSE | High	0 (NA)	MMSE | High	0 (NA)
AD Med | No	-1.9626 (0.7593)	AD Med | No	-1.2737 (0.9078)
AD Med | Yes	0 (NA)	AD Med | Yes	0 (NA)
ApoE Allele | 1	NA (NA)	ApoE Allele | 1	-0.6596 (0.5268)
ApoE Allele | 2	NA (NA)	ApoE Allele | 2	0 (NA)
Visit Week | 13	1.1309 (0.9812)	Visit Week | 13	0.2257 (1.2464)
Visit Week | 26	-0.09650 (0.8937)	Visit Week | 26	-1.4345 (1.1145)
Visit Week | 39	-0.5595 (0.7890)	Visit Week | 39	-1.7955 (1.0306)
Visit Week | 52	-1.5227 (0.7093)	Visit Week | 52	-0.3949 (0.9196)
Visit Week | 65	-0.01596 (0.7082)	Visit Week | 65	-1.3741 (0.8406)
Visit Week | 78	0 (NA)	Visit Week | 78	0 (NA)
Baseline * Visit Week | 13	-0.3528 (0.04226)	Baseline * Visit Week | 13	-0.3349 (0.05047)
…	…	…	…
Baseline * Visit Week | 65	-0.05971 (0.03107)	Baseline * Visit Week | 65	-0.01025 (0.03470)
Baseline * Visit Week | 78	0 (NA)	Baseline * Visit Week | 78	0 (NA)

Table-1. Fitted disease progression model for ADAS-Cog/11 (Alzheimer's Disease Assessment Scale–cognitive subscale, 11-item version).

Exposure response

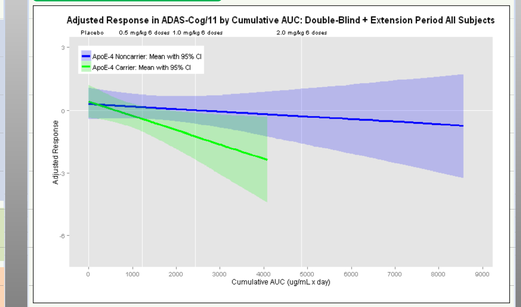


Figure-4. Exposure response in ADAS-Cog/11: double-blind + extension period.

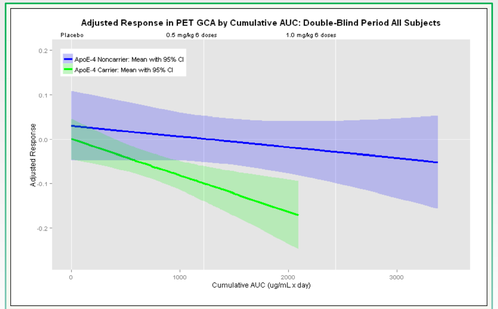


Figure-5. Exposure response in brain amyloid burden based on PET (positron emission tomography).

Summary

- A model-based approach is developed to assess the relationship between cumulative drug exposure and cumulative drug effect.
- The proposed method accounts for confounding factors such as natural disease progression and dropout, typically observed in chronic degenerative diseases.
- In practice the disease progression model can be constructed via different methods, eg, MMRM based on placebo data.
- The model-adjusted measure is used to assess the exposure response, and to provide insights to alternative data interpretation.
- Potential limitations may include:
  - interpretation of cumulative AUC: jointly impacted by multiple factors (eg, dose level, number of doses, clearance, body weight, etc)
  - study design: subject randomization to multiple AUC levels might not be random
  - methodology bias: use of a particular disease progression model
  - selection bias: incomplete control of dropout effect

References

1. Lee H, Kimko H, Rogge M, et al. Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. *Clinical Pharmacology & Therapeutics*. 2003; 73(4): 348-365.
2. Hutmacher M, Nestorov I, Ludden T, et al. Modeling the exposure-response relationship of etanercept in the treatment of patients with chronic moderate to severe plaque psoriasis. *J. Clin. Pharmacol*. 2007; 47: 238-348.

Acknowledgments

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