Towards a useful model for pseudo atrophy correction in monoclonal antibody clinical trials on Alzheimer's disease

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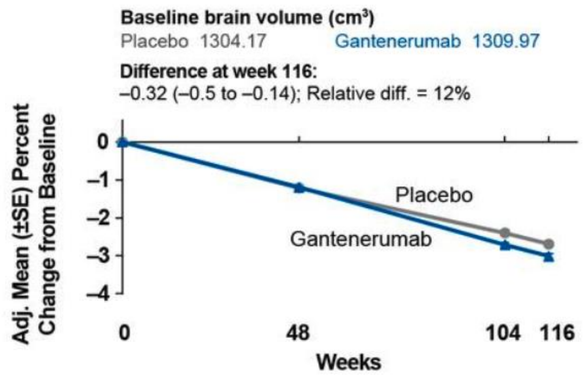
Background

- ARPA: Amyloid-removal Related Pseudo Atrophy
- Volume loss in treatment arm exceeds placebo arm (e.g., whole brain GM)

$$\hat{V}(t) \equiv \frac{1}{V_0}\left(V(t) - V_0\right) \qquad \text{eq. (1)}$$

GRADUATE I [1]



- Current thinking[2]: caused by dissolution of amyloid plaques and their conjoining gliosis-related or inflammation-related supportive tissue

We developed a computational model of *atrophy* rates as a function of amyloid level, trained on ADNI data

Objectives

1. Develop a **mathematical model of amyloid-related atrophy rates**
2. Predict atrophy outcomes in recent MAB trials

***Ultimate goal**: a model for adjusting volumetric biomarkers in trials*

The Model, part 1: Atrophy Equation

Differential Equation: brain volume as function of amyloid level:

Atrophy rates
amyloid-independent | amyloid-dependent

C = Centiloids (for convenience)

$$\frac{dV(t)}{dt} = -\alpha\left(r + aC(t)\right)V(t)$$

Trial-specific calibration factor based on placebo arm

Placebo arm atrophy rate

$$\alpha \equiv \frac{R_\mathrm{P}}{r + aC_\mathrm{P}(t)}$$

Adjustment by the placebo arm allows for demographic/etc. differences between the trial and the model training data used to estimate r and a (see **Model, part 2**).

Substitute in for α:

$$\frac{dV(t)}{dt} = -R_\mathrm{P}\frac{r + aC(t)}{r + a_\mathrm{P}C_\mathrm{P}(t)}V(t)$$

Take **linear approx**. (OK for 2–3 years**):** $C \approx \bar{C}$ (avg. CL), and **solve the DE**:

$$\hat{V}_{TX}(t) = -R_\mathrm{P}\frac{r + a\bar{C}_{TX}}{r + a_\mathrm{P}\bar{C}_\mathrm{P}}t$$

Key:
- Measurement/observation
- Amyloid-independent atrophy
- Amyloid-related extra atrophy
- TX: randomised arm
- P: placebo arm

Cases:
- $\bar{C}_\mathrm{A} \approx \bar{C}_\mathrm{P}$: no pseudo atrophy; identical placebo/active curves
- $\bar{C}_\mathrm{A} < \bar{C}_\mathrm{P}$ (amyloid removal) => predicts slower atrophy in active arm
- $C \equiv C_\mathrm{P}$: predicts the observed placebo arm atrophy (R_P)

The Model, part 2: Parameter Estimation

Our atrophy equation has parameters, which we estimate from ADNI observational data using a:

Linear Mixed Model for volume change over time.

- LMM Parameters:
  - V_0: grand intercept volume
    + random effect == individual-level ***i*** (visit ***j***)
    + adjusted for AGE, SEX, ICV (intracranial volume == head size)
  - r: atrophy rate, **amyloid-independent** (at "normal amyloid level")
    + *random effect == individual-level atrophy*
  - a: *additional* atrophy rate, due to additional amyloid
    + *random effect == individual-level atrophy*

$$V_{ij}(t) = V_0 - rt_{ij} - aC(t_{ij})t_{ij} + \beta_{\mathrm{age}}\mathrm{age}_i + \beta_{\mathrm{sex}}\mathrm{sex}_i + \beta_{\mathrm{ICV}}\mathrm{ICV}_i + b_{0i} + b_{1i}t_{ij} + \epsilon_{ij},$$

Notes:
- Amyloid $C(t_{ij})$ is measured in CL for definiteness
- Fit restricted to 120 weeks (≥ most MAB trials)
- Does not include diagnostic group

Results

LMM fitting (ADNI data: 215 A+, 180 A–)

- Amyloid-independent **whole-brain** atrophy: $r = 6.6$ mL/year
- ~1% increase in atrophy per Centiloid > 0: $a = 0.063$ mL/year/CL

Table 1. End of trial volume: Active minus Placebo

- Positive => favours treatment
- Negative => favours placebo (pseudo atrophy)

Trial	Duration (weeks)	Amyloid removal (Active arm)	Model prediction	Reported ARPA
GRADUATE-I (gantenerumab)	116	$94 \rightarrow 28$ CL	+5.8 mL	– 4.2 mL
TRAILBLAZER-ALZ-2 (donanemab)	76	$103 \rightarrow 16$ CL	+5.5 mL	– 6.5 mL
EMERGE (aducanumab)	78	$76 \rightarrow 14$ CL	+3.8 mL	– 2 mL*
GRADUATE-II (gantenerumab)	116	$96 \rightarrow 40$ CL	+3.6 mL	– 4.7 mL
ENGAGE (aducanumab)	78	$77 \rightarrow 23$ CL	+3.2 mL	– 0 mL*
CLARITY-AD (lecanemab)	79	$78 \rightarrow 19$ CL	+2.5 mL	– 4.1 mL

* ARPA estimated (not reported by the study)

Observations:
- The model always predicts lower atrophy in the placebo arm
  => because amyloid was always removed in these trials, and amyloid increases atrophy
- It's not (yet!) designed to be a directly-applicable "correction" to ARPA

Discussion

- A fun model that separates amyloid-related atrophy from amyloid-independent atrophy
- Could it be operationalised in clinical trials?
  - Maybe — depends on what we (and regulators!) want to see in volumetric outcomes
- Nothing mechanistic in the model
  - We still don't understand exactly what happens to brain tissue when amyloid plaques are dissolved, c.f., ENGAGE vs EMERGE or GRADUATE I vs II
  - Let alone differences between drugs…

NEXT STEPS:
- Consider mechanisms?
- Operationalise? Individual-level: adjust measured brain volume(s) by random effects

References:
[1] *(gantenerumab):* ***Bateman, et al., NEJM 389, 1862 (2023); DOI: 10.1056/NEJMoa2304430***
[2] ***Barkhof and Knopman, Neurology 100, 942 (2023); DOI: 10.1212/WNL.0000000000207268***
[3] *(donanemab):* ***Sims, et al., JAMA (2023); DOI:10.1001/jama.2023.13239***
[4] *(aducanumab):* ***Budd Haeberlein, et al., J Prev Alz Dis (2022); DOI:10.14283/jpad.2022.30***
[5] *(lecanemab):* ***van Dyck, et al., NEJM 388, 9 (2023); DOI:10.1056/NEJMoa2212948***

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