Exploring Amyloid Antibodies Treatment Guidelines in Alzheimer's Disease Using A Quantitative Systems Pharmacology Approach

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Poster P3-839

Background

Aducanumab and lecanemab are FDA approved, Donanemab likely to be approved soon.

These antibodies differ in biomarker changes and ARIA-E side effects due to differences in PK properties and affinity towards various Abeta forms.

Patients differ in their amyloid baseline load and APOE genotype

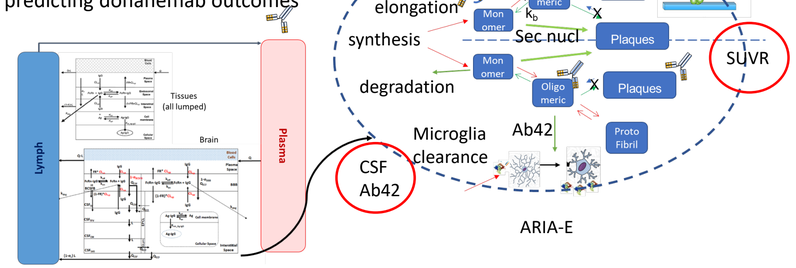
Individualized treatment guidelines include

- Halting treatment when amyloid is removed below 25 CL
- Using fluid biomarker to determine treatment duration for achieving amyloid negativity ?
- Maintenance therapy after achieving amyloid negativity
- Restarting treatment after ARIA-E detection

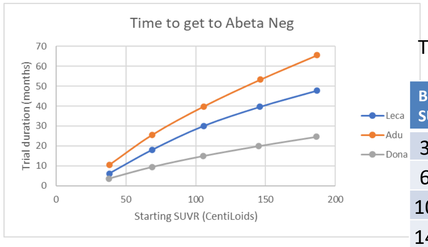
A well-validated QSP model calibrated with natural history trajectory and group-level effects of six antibodies (Geerts 2023) is used to explore optimal treatment guidelines

Amyloid-Aggregation PBPK- QSP Model

Calibrated with natural history and 6 amyloid antibodies, predicting donanemab outcomes



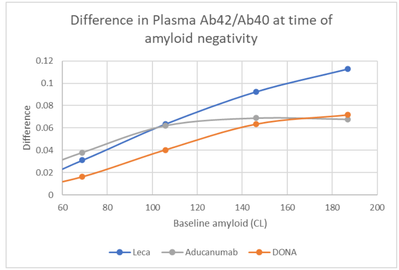
Time to reach amyloid negativity

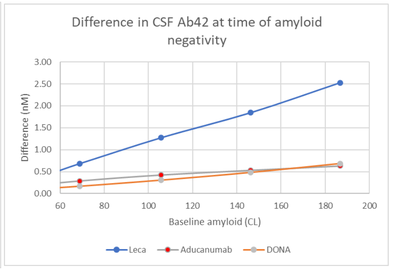


Time to reach Abeta Negativity in months

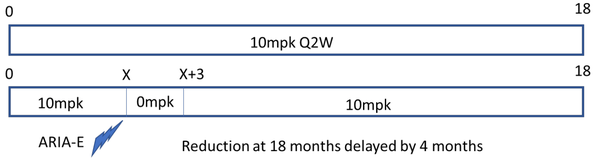
Base SUVR	Lecanemab	Donanemab	Aducanemab
38.10	6.12	3.67	10.56
68.76	18.00	9.49	25.56
105.54	30.00	14.95	39.84
145.74	39.60	19.94	53.28
186.63	47.76	24.58	65.52

Abeta fluid biomarkers at time of amyloid negativity

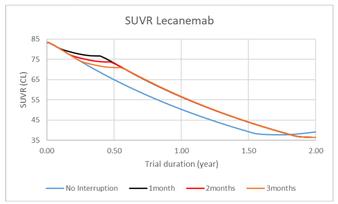




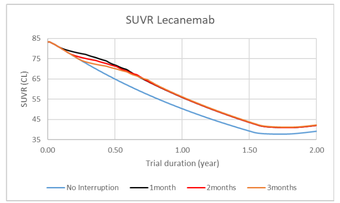
Effect of ARIA-E interruption and restart treatment



No Titration after restart

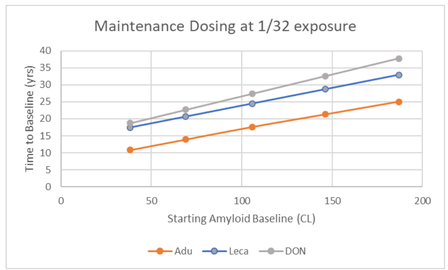


Titration after restart



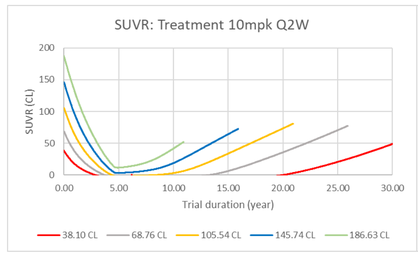
Titration results in 1.7 (dona) to 6.2 (adu) month delay in achieving amyloid negativity

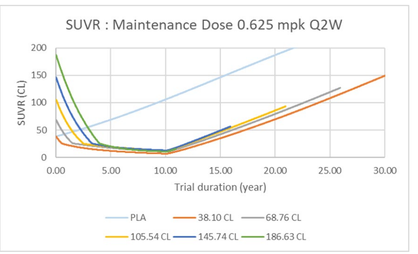
Time to reach original baseline SUVR after treatment halt



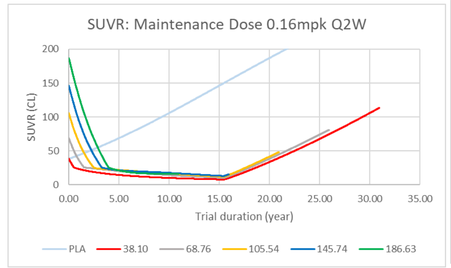
Antibodies are dosed therapeutically to achieve amyloid negativity.
Maintenance dose at 1/32 exposure runs until 10 years after trial start. Indicated times are counting from maintenance treatment halt
Most durations are beyond the lifetime of the patients

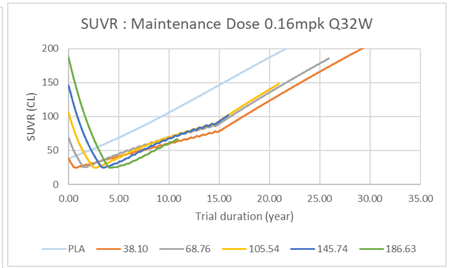
Maintenance Dosing : Change dose/Frequency





Leca 10mpk Q2W until amyloid negativity; maintenance until 10 yrs at 10mpk (left) and 0.625 mpk Q2W (right)





Leca 10mpk Q2W until amyloid negativity; maintenance treatment until 15 yrs at 0.16mpk Q2W (Left) and Q16W (right)

Discussion

For any baseline amyloid load, donanemab reaches amyloid negativity faster than lecanemab and much faster than aducanumab
Fluid biomarkers (CSF Ab42 and plasma Ab42/Ab40 ratio) to detect central amyloid negativity are much more sensitive for lecanemab than donanemab and aducanumab
Lecanemab's targets (oligomers and protofibrils influence monomer dynamics to a greater extent compared to Dona and Adu that preferentially target plaques.
Restarting treatment after ARIA-E incident can be done safely with slower titration and results in an additional 1.7 (donanemab), 3.0 (lecanameb and 6.2 month (aducanemab) delay in reaching amyloid negativity.
Maintenance dosing can be safely achieved at 32-fold lower drug exposure, either by reducing dose or frequency for 10 years
Return to baseline after halting maintenance treatment is beyond lifetime of patient

References

- Geerts et al 2023, CPT:PSP 12, 444
- Mintun et al 2022 NEJM; 384, 1691
- Van Dyck et al 2022 NEJM; 388,9