Amyloid PET Depleted Patients After Anti-Amyloid Therapies

Workgroup members

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Background

- Anti-amyloid therapies have a major effect on amyloid-PET.
- In phase 2 and 3 trials, many patients have become amyloid-PET negative after treatment.
- The observed effect on amyloid PET is thought to underpin clinical benefit.
- In donanemab phase 2 and 3 trials, set criteria for amyloid-PET negativity in previously amyloid-PET positive patients led to the patient being switched to placebo.

Specific issues and workgroup goals

Issues

- There is major heterogeneity in the definition and reporting of cases across studies, with cases identified based on PET quantification with threshold (SUVR, Centiloid) or visual read.
- As a result, there is a need for a specific name for this new entity of amyloid-negative patients with Alzheimer's disease.

Goals of the workgroup

- To summarize current knowledge about "amyloid-depleted" cases.
- To define a framework for:
    - a harmonized definition and operationalization for future studies.
    - a nomenclature for this new entity.

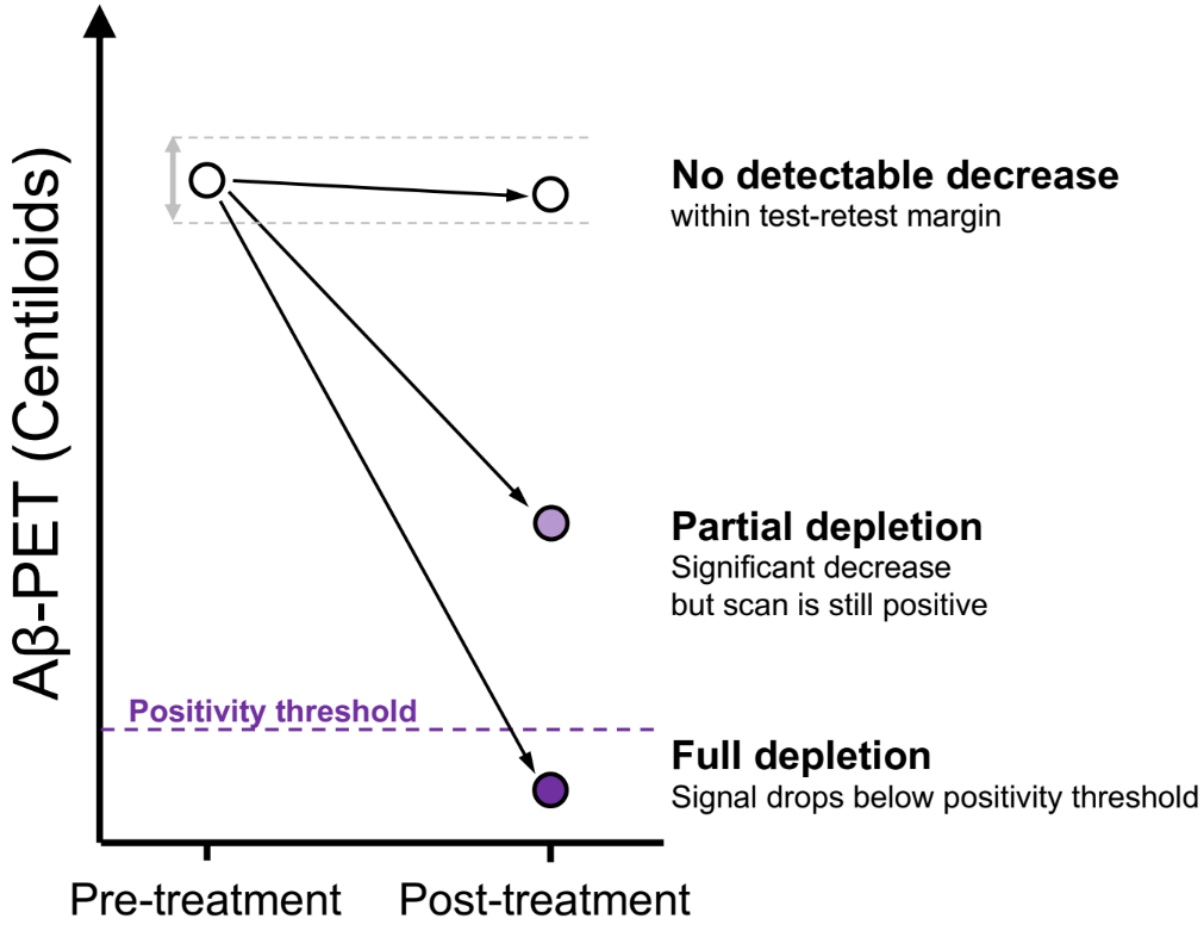
Scope of work

Our current focus is on:

- Data available in disease modifying therapies in cognitively impaired patients (not preclinical AD).
- Defining group based on amyloid-PET (not other biomarkers):
    - PET has been the gold standard in trials so far.
    - PET quantification is more harmonized than CSF/plasma measures.
    - Changes in biofluid biomarkers have been reported, but not with the same level of detail as PET.
    - We plan to document the currently known course of fluid biomarker changes in our report.

Implementation: Proposed 3-tier classification

Suggestions for standard reporting in research studies, clinical trials and clinical practice (when data available).



Define a positivity threshold?

Amyloid deposition is a continuous process and studies have shown "subthreshold effects" at the group level. But thresholds would allow ease of employment and cross-comparison across clinical trials, research studies and clinical settings, similar to what the AT(N)/NIA-AA framework did.

To determine thresholds that could be usable across contexts of use, the workgroup considered threshold(s) reported in the literature based on various gold standards.

- Thresholds to define amyloid positivity in observational studies and trials:
  - ADNI (18-20, see Royse 2021)
  - AHEAD A3 inclusion > 20 (intermediate amyloid range defined as [20-40])
- Centiloid values corresponding to visual read
  - 16 Matsuda 2021
  - 17 Collij 2021
  - 21 Collij 2023
  - 24.6 (IDEAS, CTAD23)
- Data driven approaches
  - 19 - reliable worsening cut point (Mayo) Jack 2017
- Thresholds used in anti-amyloid trials to define amyloid negativity after treatment:
  - Aducanemab (ENGAGE/EMERGE): 20.2 CL (CTAD 2023)
  - Lecanemab (Clarity-AD): 30 Van Dyck 2023
  - Donanemab (Trailblazer-Alz2): 24.1 Sims 2023

Thresholds seem to converge around 20 CL, but similar to the AT(N) framework, individual groups will be able to apply their own method.

Regarding implementation

Implementation could be relatively easy in research studies and trials, as Centiloids are now widely used.

However, there would be multiple issues in clinical settings, as

- Questions remain regarding collection of longitudinal scans clinically
- Amyloid-PET is currently only approved for visual (binary read); no quantification method is currently approved.
- With regard to the visual interpretation of post DMT Amyloid-PET, it is not yet known if there are any specific characteristics to consider when visually interpreting a post-DMT scan? I.e., are they similar to 'wildtype' amyloid negative scans? Do ARIA impact PET tracer binding?

Nomenclature (work in progress)

3 components are being considered for naming, to indicate:

- Change compared to prior
    - *Change / Depletion / Reduced / Clearance*
- Change in response to treatment
    - *Treatment-induced / Following treatment / After treatment / Response*
- Change is in biomarker, not necessarily pathology
    - *Amyloid biomarker* or specific to modality (PET versus fluid)

Examples of terms that combine all components:

"Treatment-Induced Amyloid Biomarker Depletion"
"Reduced Amyloid Biomarker After Treatment"...

An umbrella term to more broadly describe individuals who display changes in biomarkers following treatment is also under consideration.

Current evidence and gaps in knowledge

Questions remain regarding

- The underlying neuropathology: very limited data.
- The relationship with biofluid markers.
    - Difference in time course? Are fluid biomarkers "normalizing" like PET does?
- Predictors of Amyloid-PET depletion?
    - From (few) publications: baseline Amyloid levels, treatment dose and duration.
- Factors associated with Amyloid-PET depletion.
    - Clinical response, future change in biomarkers.
- The management of amyloid depleted patients?
    - Adapt treatment duration?
    - Enrollment in other trials?
    - Relevance to combination approach?

Feedback is needed

We invite comments and feedback, particularly seeking suggestions regarding:

- the relevance and usefulness of the 3-tiers classification framework (Proposed 3-tier classification)
- the possibility of defining a harmonized threshold for amyloid-PET negativity following treatment (Define a positivity threshold?)
- the name of this entity (Nomenclature)