Microdigest 1

Round-up of AD/PD and CONy

Here we summarize the key data releases or discussion topics from AD/PD 2024 and CONy 2024 focusing on novel biomarkers and anti-amyloid therapies.

AD/PD™ 2024
Lisbon, Portugal
5-9 March

CONy 2024
London, UK,
21-23 March

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Biomarkers

Key takeaways:

- Blood-based biomarkers, primarily p-tau, strongly correlate with PET amyloid-beta levels.
- Potential for blood-based biomarkers to distinguish patients with Alzheimer's disease (AD) from controls at various stages of the disease continuum (or at least their risk for) and for prescreening in trials to avoid the need for PET/CT, saving costs and reducing enrolment times.
- Blood-based biomarker results may be affected by age, BMI, sex, race, and creatinine levels.
- Blood-based biomarkers are helpful in patients with subjective cognitive decline, but it is too early for mass or pre-clinical testing.

p-tau

Comprehensive mass spectrometric analysis of plasma tau species in relation to neuropathology and clinical evaluation (AD/PD; ID 2302)

Presenter: Laia Montoliu-Gaya (Sweden)

- Study of six p-tau proteins (p-tau 181, 199, 202, 205, 217 and 231) in brain donors with and without AD.
- The ratio of plasma p-tau 217 to 212-221 showed the highest accuracy (96%) in detecting AD, including discrimination of cases concurring with co-pathologies, and could mitigate the impact of CDK.

Plasma p-tau 217 superiority compared to other plasma biomarkers in prediction of amyloid PET positivity in tertiary memory clinic patients (AD/PD; ID 1768)

Presenter: Marco Bucci (Sweden)

- Comparison of p-tau 217, p-tau 181, p-tau 231, and GFAP.
- p-tau 217 was the most closely correlated with beta-amyloid PET levels and was most accurate at identifying patients who were beta-amyloid positive, at 93.1%, followed by GFAP at 78.0%, p-tau 231 at 68.9%, and p-tau 181 at 67.8%.
- Accuracy increased to 97.5% with p-tau 217 plus all the biomarkers plus neurofilament light, amyloid-beta 40, and amyloid-beta 42. In the absence of p-tau 217, predictive accuracy was 85.9%, which did not differ significantly from that of p-tau 217 alone.

Targeting multiphosphorylated tau: Plasma tau simultaneously phosphorylated at T217 and T231 surpasses performance of p-tau 217 (AD/PD; ID 149)

Presenter: Anna Lidia Wojdała (Netherlands)

- An assay detecting plasma tau simultaneously phosphorylated at T217 and T231 (C231D217) distinguished patients with preclinical AD from controls with an accuracy of 91%. This compared with respective accuracies of 85% and 77% for singleplex plasma p-tau 231 and 217.
- Similarly, plasma C231D217 identified 100% of 21 individuals with MCI/AD from controls, while plasma p-tau 231 identified 97% of individuals and plasma p-tau 217 identified 90%. The corresponding accuracies for identifying 19 individuals with AD dementia from controls were 100% versus 92% and 91%.

Plasma p-tau 212 is associated with cognitive decline and disease progression in cognitively unimpaired people (AD/PD; ID 1562)

Presenter: Przemyslaw Kac (Sweden)

- Plasma p-tau 212 at baseline was significantly associated with the modified Preclinical Alzheimer's Cognitive Composite in people without cognitive impairment in the Biofinder-1 cohort and was significantly associated longitudinally with an increased risk for conversion to AD-dementia, with an HR of 2.62 and 2.3 after adjustment for amyloid-beta positivity.

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Plasma p-tau 217 as a screening tool for Aβ-PET in clinical trials across the AD continuum (AD/PD; ID 2392)

Presenter: Pamela Lukasewicz Ferreira (USA)

- Plasma p-tau 217 as a screening tool, reducing the need for amyloid-beta PET scans.
- In 808 amyloid-positive cognitively unimpaired individuals, a liberal p-tau 217 cutoff of 0.32 pg/mL reduced the number of required amyloid-beta PET scans by 42%. This increased to 64% and 75% reductions with intermediate and conservative cutoffs of 0.48 and 0.65 pg/mL, respectively.
- In 916 amyloid-positive cognitively impaired individuals, amyloid-beta PET scans were avoided in 24%, 47%, and 52% of patients at cut-offs of 0.19, 0.47, and 0.76 pg/mL, respectively.
- The greatest cost savings were estimated to be 40% and 15% in the two groups, respectively.

Performance of blood-based biomarker prescreening in the SKYLINE secondary prevention phase 3 study with gantenerumab (AD/PD; ID 589)

Presenter: Tobias Bittner (Switzerland)

- Using Elecsys® Phospho-Tau (181P) and Apolipoprotein E4 plasma prototype assay, increased the identification of amyloid positive patients.
- In the secondary prevention phase 3 study, identification increased from 12.3% with CSF/PET to 19.3%.
- Prescreening avoided the need for more than 40% of downstream screening assessments, such as cognitive batteries, magnetic resonance imaging, and PET/CSF testing, without ruling out many true high-amyloid individuals (negative predictive value of 98%).

NfL

Development of a prototype point-of-care test with FOPPR technology for ultrasensitive detection of neurofilament light chain in plasma (AD/PD; ID 1418)

Presenter: Madison Honey (Netherlands)

- The prototype Fiber Optic Nanogold-linked Immunosorbent Assay (FONLISA) based on fiber optic particle plasmon resonance technology showed feasibility for the ultrasensitive measurement of NfL in ethylenediamine tetraacetic acid plasma when tested in patients with AD versus controls.
- Holds promise for point-of-care application following further optimization to improve technical stability and analytical sensitivity.

GFAP

Relationship of plasma NfL, GFAP, Aβ1-42/Aβ1-40 and p-tau 181 with synaptic density and Alzheimer's disease hallmarks in non-demented older adults (AD/PD; ID 124)

Presenter: Steffi De Meyer (Belgium)

- Higher plasma GFAP was significantly associated with lower synaptic density, which was partially mediated (20%) by a reduction in neurofibrillary tangles in limbic structures. This association was independent of amyloid load and there was no association between p-tau 181 and synaptic density.

Anti-amyloid therapies

Key takeaways:

- Superior amyloid clearance with donanemab versus aducanumab.
- Potential for improved outcomes with earlier treatment in patients before cognitive symptoms appear, as indicated by low versus high levels of tau.
- Extending treatment of lecanemab beyond 18 months shows efficacy in statistical modelling but clinical evidence is still lacking.
- Baseline PET amyloid shows potential for predicting amyloid clearance.
- Future may lie in combination therapies based on anti-amyloid medications.

Donanemab

TRAILBLAZER-ALZ 4: Donanemab vs aducanumab 18-month results

TRAILBLAZER-ALZ 4: Directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease - results from 18-months (AD/PD; ID 2573)

Presenter: Stephen Salloway (USA)

- At 18 months, amyloid clearance (<24.1 CL) in 77.5% of donanemab-treated patients versus 42.5% of aducanumab-treated patients; significant difference ($p<0.001$).
- In patients with low-to-medium tau at baseline (tau standardized reuptake value of >1.10 and ≤1.46), 77.0% of donanemab-treated patients achieved amyloid clearance vs 34.6% of aducanumab-treated patients; significant difference ($p=0.022$).
- Amyloid levels decreased from baseline by a least squares mean of 86.3 centiloids with donanemab, which was significantly greater than the 72.8 centiloids achieved with aducanumab.
- Lower rates of treatment-emergent ARIA-E with donanemab: 23.9% vs 34.8%.

TRAILBLAZER-ALZ analysis: Correlations between plasma biomarkers and amyloid clearance

Advances in our understanding of amyloid plaque clearing therapies (AD/PD; ID 113)

Presenter: Mark Mintun (USA)

- Early changes in amyloid clearance and plasma biomarkers are positively correlated. However, ability for plasma biomarkers to predict the clearance of amyloid is limited currently.
- Among donanemab-treated patients, amyloid clearance at 24 weeks was predicted by:
  - p-tau 181 with 64% accuracy
  - p-tau 217 with 66% accuracy
  - GFAP with 57% accuracy
  - All three combined with 68% accuracy
- And amyloid clearance at 52 weeks by:
  - p-tau 181 with 61% accuracy
  - p-tau 217 with 64% accuracy
  - GFAP with 60% accuracy
  - All three combined with 66% accuracy
- Donanemab treatment delays loss of independence (CDR-SB=11) by 37.3 months versus placebo among patients with low-to-medium tau and by 4.6 months in those with high tau.

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TRAILBLAZER-ALZ 2 post-hoc analysis: Factors associated with amyloid clearance (<24.1 CL)

Baseline characteristics associated with achieving rapid amyloid plaque clearance following donanemab treatment (AD/PD; ID 1274)

Presenter: Sergey Shcherbinin (USA)

- Of 41 baseline factors, five were identified as associated with predicting amyloid clearance at 24 weeks (81% accuracy):
  - Baseline PET amyloid and tau level
  - Age
  - Bodyweight
  - APOE 4 genotype
- Baseline amyloid level was the strongest single predictor – 73% accuracy.
- Significant odds ratios TRAILBLAZER-ALZ 2:
  - Amyloid (≥118 CL vs <86 CL) = OR 0.12
  - Age (≥76 years vs <70 years) = OR 4.85
  - Tau PET (≥1.77 vs <1.44 CL) = OR 0.40
  - Bodyweight (≥78 vs <64 kg) = OR 0.49
  - APOE 4 (homozygous vs noncarrier) = OR 0.37

Lecanemab

CLARITY AD: Extension phase

Lecanemab for the treatment of early Alzheimer's disease: the extension of efficacy results from CLARITY AD (AD/PD; ID 2911)

Presenter: Christopher Van Dyck (USA)

- During the open-label phase from 18 to 24 months, the difference between the disease trajectories for patients initially treated with lecanemab and those treated with placebo remained parallel and the significant difference on the CDR-SB, ADAS-cog14, and ADCS MCI-ADL remained.
- In a historical control group (Alzheimer's Disease Neuroimaging Initiative) matched to the CLARITY AD population for baseline demographics and clinical characteristics, the disease trajectory was similar to that of the CLARITY AD placebo group out to 18 months but then showed "an acceleration of decline" between 18 and 24 months, whereas switching to lecanemab was associated with more disease stability.

Exploratory findings for earlier stage of treatment

- At 18 months, an estimated 93.3% of 42 patients with low baseline tau PET (<1.06 SUVr) had amyloid PET clearance (<30 centiloids), compared with 56.9% of 37 patients with intermediate-to-high tau PET (1.06 to >2.91 SUVr) and 71.8% of 79 patients in the whole tau PET subpopulation.
- This suggests that "individuals with low tau – and thus at an earlier pathogenetic stage – show clinical stability or improvement," which raises "the question of whether patients at the early pathogenetic stage may benefit more".
- Analyzing a similar stage of disease based on an amyloid PET level <60 centiloids for the whole CLARITY AD population showed less decline on the CDR-SB, ADAS-cog14, and ADCS MCI-ADL at 18 months with lecanemab than placebo, at 51%, 69%, and 72%, with the suggestion of continued benefit from lecanemab through 24 months.

Substudy of effect on tau accumulation

Treatment with lecanemab disrupts tau accumulation across brain regions in early Alzheimer's disease (AD/PD; ID 2334)

Presenter: Arnaud Charil (USA)

- At baseline, tau levels were high particularly in early temporal brain regions and were higher in individuals who also had increased amyloid levels.
- Without treatment, higher tau PET at baseline was associated with increased tau accumulation across brain regions as disease progressed. By contrast, treatment with lecanemab slowed tau progression in the medial temporal regions relative to placebo.

Other anti-amyloid therapies

GANTENERUMAB/SOLANEZUMAB

Anti-amyloid-beta treatment effects on dominantly inherited Alzheimer autopsy findings from the DIAN-TU-001 trials of gantenerumab or solanezumab (AD/PD; ID 2556)

Presenter: Charles Chen (USA)

- Preliminary autopsy findings from the trial showed gantenerumab-treated patients versus non-treated/placebo-treated patients had less amyloid-beta aggregation in 10 neuroanatomical regions of interest, with evidence of a dose-dependent effect. However, complete elimination was not achieved.
- Fractions of tau pathology, microglia, or astrocytes were unaffected.

ADUCANUMAB

Aducanumab treatment modulates microglial activation in a sex dependent manner (AD/PD; ID 2524)

Presenter: Lis De Weerd (Germany)

- Removal of amyloid-beta with aducanumab is associated with a reduction in microglial response in the brains of APP-SAA triple knockout mice, as measured by TREM2 and soluble (s)TREM2.
- Showing a link between anti-amyloid treatment and immune cell function is a step to better understanding how treatment is associated with adverse effects such as ARIA-H and E.
- The same association was also seen for sTREM2 in the CSF, but only in male mice.

TRONTINEMAB

Rapid dose-dependent amyloid plaque depletion with trontinemab, a novel brainshuttle™ antibody development for the treatment of Alzheimer's disease (AD/PD; ID 2578)

Presenter: Luka Kulic (Switzerland)

- Cohort 3: Intravenous trontinemab 1.8 mg/kg (n=13) versus placebo (n=12) every 4 weeks.
- Mean amyloid PET reductions from baseline (100 centiloids) of 60 centiloids at 12 weeks and 91 centiloids at 28 weeks. At 28 weeks, PET scans for 8 patients showed 75% were amyloid negative (≤24 centiloids).
- Cohort 4: Interim analysis for 12 patients randomly assigned to trontinemab 3.6 mg/kg show a reduction in mean amyloid PET at 12 weeks of 98 centiloids (119 centiloids at baseline) and 5 (63%) of 8 patients amyloid negative.
- Low ARIA-E and ARIA-H incidence: 6.7% overall for cohort 3 and none in cohort 4 so far.