17th Clinical Trials on Alzheimer's Disease conference (CTAD), 29 October – 1 November 2024, Madrid, Spain

Revamping Alzheimer's disease diagnostics: evaluating future IVD plasma p-Tau 181 and ApoE4 immunoassays for amyloid detection in a multi-centre study reflective of routine clinical practice

Imke Kirste,[1] Sayuri Hortsch,[2] Sheila Baez-Torres,[3] Mercè Boada,[4] Monica Crane,[5] Kristian Steen Frederiksen,[6] Kevin Hanson,[7] Jonathan Liss,[8] Jeffrey Norton,[9] Marc Suárez-Calvet,[10] Craig Ritchie,[11] Stephanie Rutrick,[12] David Watson,[13] Kelley Yokum,[14] Clara Quijano-Rubio[15]

[1]Roche Molecular Solutions, Indianapolis, USA; [2]Roche Diagnostics GmbH, Penzberg, Germany; [3]K2 Medical Research, Maitland, USA; [4]ACE Alzheimer Center, Barcelona, Spain; [5]Genesis Neuroscience Clinic/Tennessee Memory Disorders Foundation, Knoxville, USA; [6]Danish Dementia Research Centre, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; [7]Eastside Research Associates, Redmond, USA; [8]Columbus Memory Center, Columbus, USA; [9]Charter Research Lady Lake, The Villages, USA; [10]Barcelona Beta Brain Research Center, Barcelona, Spain; [11]Scottish Brain Sciences, Edinburgh, UK; [12]Adams Clinical, Watertown, USA; [13]Alzheimer's Research and Treatment Center, Wellington, USA; [14]K2 Medical Research, LLC, Tampa, USA; [15]Roche Diagnostics International Ltd, Rotkreuz, Switzerland

Poster no. LP065

Introduction

- Early detection of Alzheimer's disease (AD) by recognizing the presence of β-amyloid is critical for diagnosis.[1] Blood-based biomarkers have emerged as powerful tools in accurately identifying amyloid pathology.[2]
- Plasma biomarkers included in the Elecsys® Amyloid Plasma Panel (tau phosphorylated at threonine 181 [p-Tau 181] and apolipoprotein E4 [ApoE4p]; Roche Diagnostics International Ltd, Rotkreuz, Switzerland) correlate with β-amyloid positivity detected by cerebrospinal fluid (CSF) biomarkers and amyloid-positron emission tomography (PET) in individuals with cognitive complaints or impairment.[3]
- This study investigated the clinical performance of plasma p-Tau 181 in combination with plasma ApoE4p (Elecsys Amyloid Plasma Panel), and plasma p-Tau 181 alone, as potential *in vitro* diagnostics (IVDs) to rule out amyloid pathology, and addressed gaps in evidence by providing blood-based biomarker data gathered from a broad population, in terms of sex, race and comorbidities, as seen in routine clinical practice.

Objective

- This study aimed to establish the Elecsys Amyloid Plasma Panel (combined plasma p-Tau 181 and ApoE4p) and the Elecsys Phospho-Tau (181P) Plasma immunoassay (plasma p-Tau 181 alone; Roche Diagnostics International Ltd) cutoffs to rule out amyloid pathology.

Methods

- In this prospective multi-centre study, patients aged 55–80 years with cognitive complaints or objective memory impairment with unknown symptom aetiology and where a diagnostic workup for AD or other causes of cognitive decline was relevant but not performed, were enrolled.
  - The study population, including patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI) or mild dementia, was recruited at 12 clinical sites (research, secondary and tertiary) in the United States (US) and Europe.
- Plasma samples from eligible patients were analysed using the Elecsys Phospho-Tau (181P) Plasma and Elecsys Apolipoprotein E4 Plasma immunoassays (Roche Diagnostics International Ltd).
- The clinical performance of the Elecsys Amyloid Plasma Panel, and the Elecsys Phospho-Tau (181P) Plasma immunoassay alone, was assessed with respect to amyloid-PET visual read (18F-Florbetapir, 18F-Florbetaben or 18F-Flutemetamol) and the CSF ratio measured by the Elecsys Phospho-Tau (181P) CSF and Elecsys β-Amyloid (1-42) II CSF immunoassays (Roche Diagnostics International Ltd).
  - Sensitivity, specificity and positive and negative predictive values (PPV and NPV, respectively) were calculated.
- Concordance analysis between plasma ApoE4p and *APOE4* genetic status was performed.
- Exploratory analyses examined subgroup effects based on cognitive status, comorbidities and demographics.

Results

- A total of 492 patients were enrolled; 80.7% of patients were from the US.
  - Overall, 475 patients had amyloid-PET results (23.4% positive; 76.6% negative) and 360 patients had CSF results (31.9% positive; 68.1% negative); there were 343 patients with amyloid-PET+CSF crossover.
- The study population was heterogeneous regarding sex, race and comorbidities (**Table 1**), allowing for assessment of plasma p-Tau 181 and ApoE4p performance in a real-world setting.

Table 1. Baseline demographics and characteristics (N=492).

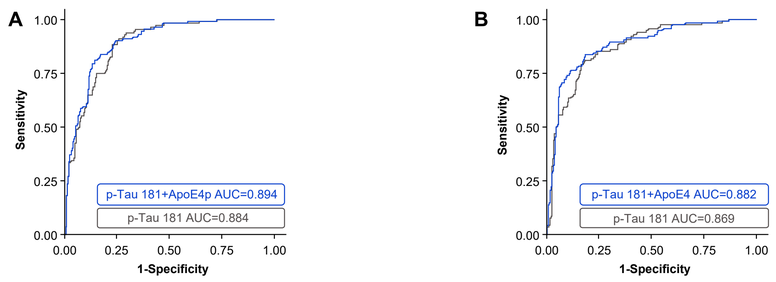
Characteristic	All patients	Characteristic	All patients	Characteristic	All patients
Age (years)		**Sex, n (%)**		**Race, n (%)**	
Mean (SD)	69.2 (6.6)	Male	185 (37.6)	White	424 (86.2)
Median (IQR)	70.0 (64.0–75.0)	Female	307 (62.4)	Asian	5 (1.0)
Range, min–max	55.0–80.0			Black/African American	54 (11.0)
				Other	9 (1.8)
Ethnicity, n (%)		**Clinical diagnosis, n (%)**		**eGFR**	
Not Hispanic or Latino	358 (72.8)	SCD	142 (28.9)	Mean (SD)	79.0 (16.8)
Hispanic or Latino	37 (7.5)	MCI	308 (62.6)	Median (IQR)	81.4 (68.4–92.2)
Not reported	2 (0.4)	Mild dementia	39 (7.9)	Range, min–max	3.4–109.0
Unavailable	95 (19.3)	Unavailable	3 (0.6)		
Plasma p-Tau 181, pg/mL		**Plasma ApoE4p, n (%)**		***APOE4* status, n (%)**	
Mean (SD)	1.14 (0.9)	Reactive	181 (36.8)	Carrier	131 (26.6)
Median (IQR)	0.9 (0.7–1.3)	Non-reactive	311 (63.2)	Non-carrier	246 (50.0)
Range, min–max	0.3–10.0			Unavailable	115 (23.4)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

Results (cont.)

- The area under the curve (AUC) for combined plasma p-Tau 181 and ApoE4p was 0.894 with respect to amyloid-PET; while plasma p-Tau 181 alone had an AUC of 0.884 (**Figure 1A**).
- The AUC for combined plasma p-Tau 181 and ApoE4p was 0.882 with respect to CSF; while plasma p-Tau 181 alone had an AUC of 0.869 (**Figure 1B**).

Figure 1. AUCs for combined plasma p-Tau 181 and ApoE4p, and p-Tau 181 alone, with respect to (A) amyloid-PET and (B) CSF.



- Based on an amyloid-PET positivity prevalence of 23.4%, the NPV for combined plasma p-Tau 181 and ApoE4p was 96.2%, with a PPV of 47.9% (**Table 2**).
  - NPV was minimally impacted by age, sex, body mass index or impaired kidney function.
- Rule-out performance of plasma p-Tau 181 alone was similar (NPV: 97.6%, PPV: 46.1%; **Table 2**).

Table 2. Performance of combined plasma p-Tau 181 and ApoE4p, and p-Tau 181 alone, with respect to amyloid-PET and CSF.

Performance measure, % (95% CI)	Estimate for combined plasma p-Tau 181 and ApoE4p	Estimate for plasma p-Tau 181
Amyloid-PET performance		
Observed prevalence	23.4 (19.8–27.4)	23.4 (19.8–27.4)
Observed NPV	96.2 (93.2–97.9)	97.6 (94.8–98.9)
Observed PPV	47.9 (41.2–54.6)	46.1 (39.7–52.5)
Sensitivity	91.0 (84.2–95.0)	94.6 (88.7–97.5)
Specificity	69.8 (64.9–74.3)	66.2 (61.2–70.9)
CSF performance		
Observed prevalence	31.9 (27.3–36.9)	31.9 (27.3–36.9)
Observed NPV	91.7 (87.1–94.7)	91.2 (86.3–94.4)
Observed PPV	62.8 (55.0–70.0)	58.7 (51.1–65.9)
Sensitivity	85.2 (77.6–90.6)	85.2 (77.6–90.6)
Specificity	76.3 (70.6–81.2)	71.8 (65.9–77.1)
Rule-out rate	55.3 (50.9–59.6)	51.6 (47.2–56.0)

CI, confidence interval.

- However, combined plasma p-Tau 181 and ApoE4p, a major genetic risk factor for AD and for adverse events of amyloid-modifying therapies, made the clinical performance more robust towards analytical variability (**Table 3**).
  - Smaller changes in predictive values following the addition of bias and coefficients of variation were observed for combined plasma p-Tau 181 and ApoE4p compared with p-Tau 181 alone.
  - Moreover, predictive values were balanced between carriers and non-carriers of the *APOE* ε4 allele when using combined plasma p-Tau 181 and ApoE4p compared with p-Tau 181 alone.

Table 3. Performance of combined plasma p-Tau 181 and ApoE4p, and p-Tau 181 alone, with respect to amyloid-PET per plasma ApoE4p status.

Performance measure	Estimate for combined plasma p-Tau 181 and ApoE4p		Estimate for plasma p-Tau 181	
	Plasma ApoE4p reactive	Plasma ApoE4p non-reactive	Plasma ApoE4p reactive	Plasma ApoE4p non-reactive
Observed prevalence, % (95% CI)	41.1 (34.1–48.5)	13.0 (9.7–17.3)	41.1 (34.1–48.5)	13.0 (9.7–17.3)
Observed NPV, % (95% CI)	97.6 (87.4–99.9)	96.0 (92.5–97.9)	95.6 (87.8–98.5)	98.3 (95.2–99.4)
Observed PPV, % (95% CI)	53.0 (44.6–61.2)	39.0 (28.8–50.1)	64.5 (55.1–72.9)	29.8 (22.3–38.4)
Sensitivity, % (95% CI)	98.6 (92.5–99.9)	76.9 (61.7–87.4)	95.8 (88.5–98.6)	92.3 (79.7–97.3)
Specificity, % (95% CI)	38.8 (30.0–48.5)	82.0 (76.9–86.2)	63.1 (53.5–71.8)	67.4 (61.5–72.8)
Rule-out rate, % (95% CI)	23.4 (17.8–30.2)	74.3 (69.1–78.9)	38.9 (31.9–46.2)	59.7 (54.0–61.5)
Simulated reduction in NPV, %*	1.6		2.4	
Simulated reduction in PPV, %†	5.6		7.6	

*Simulated change in NPV under worst-case measurement conditions with positive bias: 10%; coefficient of variation: 10%;
†Simulated change in PPV under worst-case measurement conditions with negative bias: 10%; coefficient of variation: 10%.

- In 377 patients with genotyping information available, 100% concordance was observed between plasma ApoE4p results and *APOE4* carrier status.

Conclusions

- The observed clinical performance in this study highlights the potential of the Elecsys Amyloid Plasma Panel and Elecsys Phospho-Tau (181P) Plasma immunoassay as accurate and robust tools for ruling out individuals with a low likelihood of amyloid pathology in the early stages of the AD continuum.
- Paired with high analytical performance of the plasma immunoassays, further IVD development is being pursued in an ongoing independent, prospective validation cohort.

Disclosures

- The study was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). Third-party medical writing assistance, under the direction of the authors, was provided by Sophie Lavelle, MSc, of Ashfield MedComms (Macclesfield, UK), an Inizio company, and was funded by Roche Diagnostics International Ltd.
- IK is an employee, and shareholder, of Roche Molecular Solutions. SH is an employee of Roche Diagnostics GmbH. KSF has given lectures in symposia sponsored by, and served on advisory boards for (fees paid to institution), Novo Nordisk. JL has received consultancy fees and/or research trial income from Abbvie, Accumen, Biogen, Cassava, Eisai, Eli Lilly, Merck, Prothena and Roche. MS-C has given lectures in symposia sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics and Roche Farma, has received consultancy (fees paid to institution) from Roche Diagnostics, and served on advisory boards of Roche Diagnostics and Grifols. MS-C was also granted a project by, and is a site investigator for a clinical trial (funded to his institution) for, Roche Diagnostics. In-kind support for research (fees paid to institution) was received from ADx Neurosciences, Alamar Biosciences, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development and Roche Diagnostics. CR is the CEO, founder and majority stakeholder of Scottish Brain Sciences, has received consultancy fees from Abbvie, Actinogen, Biogen, Eisai, Eli Lilly, MSD, Novo Nordisk and Roche, and has received payment/honoraria for presenting from Eisai and Roche. CQ-R is an employee of Roche Diagnostics International Ltd. The remaining authors have no conflicts of interest to report.
- ELECSYS is a trademark of Roche. The Elecsys Amyloid Plasma Panel, and the Elecsys Phospho-Tau (181P) Plasma and Elecsys Apolipoprotein E4 Plasma immunoassays, are not approved for clinical use. The Elecsys β-Amyloid (1–42) CSF II and Elecsys Phospho-Tau (181P) CSF immunoassays are approved for clinical use.

References

1. Prince M, et al. Alzheimer's Disease International: World Alzheimer Report 2011. The benefits of early diagnosis and intervention. Available at: https://www.alzint.org/u/WorldAlzheimerReport2011.pdf. Accessed September 2024.
2. Hampel H, et al. Neuron 2023;111:2781−99.
3. Blennow K, et al. Clinical performance and robustness of blood-based biomarkers for early detection of amyloid pathology associated with Alzheimer's disease. Poster 69052 at Alzheimer's Association International Conference (AAIC) 2022.

Access this poster using the quick response (QR) code or by visiting: https://ter.li/4710jp