Journey to a New Era for Alzheimer's Disease

1. AD/PD™ 2024
2. CONy 2024
3. AAIC 2024
4. CTAD 2024
   October/November – Madrid, Spain

Experts in conversation

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How can clinical trial data and real-world experience aid timely diagnosis and safer integration of amyloid-targeting therapies in all populations?

Summary Slides

CME

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More timely diagnoses in all populations



What happened at CTAD?

1 AD/PD
2 CONy
3 AAIC
4 **CTAD**

Data on improving representation and diversity in clinical trials and potential utilization of blood-based biomarkers in primary care is providing hope for more timely diagnosis in both general and under-represented populations.

Expert insights

- Underrepresentation of minority groups in clinical trials has been a longstanding problem but there is hope that the integration of blood-based biomarkers will improve this.
  - Black and Hispanic groups are particularly under-represented due, in part, to hesitancy around invasive procedures (e.g., lumbar punctures) and PET scans.
  - Screening in these populations showed lower amyloid positivity rates than anticipated as these groups generally have a higher rate of cognitive impairment.
  - Blood tests worked well in these populations, with amyloid PET data demonstrating similar rates of positivity when the blood test was positive.
- Introduction of plasma tests reduces the screening failure rate in clinical trials and works well in primary care settings.
  - Data showed plasma tests reduce the screening failure rate from 70% to 30%.
  - Early data suggest high concordance of blood test results with PET and CSF testing in primary care settings.

Utilization of blood-based biomarkers in practice



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Real-world data and research on the blood-based biomarkers in population subgroups was presented which is showing real promise of these tools for diagnosis and prognosis. Multi-analyte blood biomarker tests could further improve efficiency and utility in practice.

Expert insights

- Data from a variety of subgroups is demonstrating a high concordance of blood test results with PET and CSF testing in both primary and secondary care settings.
  - The consistency and predictive power of biomarkers like plasma p-tau 217 could improve both clinical trial recruitment and broader clinical diagnostic workflows.
- Some comorbidities (e.g. kidney disease and BMI) affect biomarker levels, but ratio-based adjustments can help correct for individual variability.
  - Numerous studies, including ADACC and AD Riddle, are investigating comorbidity effects and blood test utility across diverse populations.
- Current clinical use of blood tests is primarily for prescreening, but as availability and reimbursement improves, uptake will hopefully follow.
- Specific biomarkers (e.g., NfL) may help differentiate Alzheimer's from other conditions like frontotemporal dementia.
- Efforts are ongoing to develop biomarkers for ARIA and amyloid clearance, with blood and CSF biomarkers being explored as part of future routine assessments.
- Replacing invasive lumbar punctures and PET scans with blood tests could significantly lower diagnostic costs, especially in secondary care.

Real-world use of amyloid-targeting therapies (ATTs)



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Real-world experience and longer-term outcomes of ATTs were presented alongside appropriate use criteria. Much of the data focused on improving safety of these therapies and further refining the patient selection criteria.

Expert insights

- Real-world data indicate that ATTs are being integrated in line with their labels and that safety and efficacy outcomes are overall aligning with results from clinical trials.
  - Eligibility for ATTs in real-world practice is relatively low (approx. 10% of patients), which is due to not having AD, disease stage at presentation, comorbidities, or personal choice.
- Exclusion of APOE e4 carriers showed no significant impact on efficacy, which may in the future encourage use in these patient subgroups.
- Extension studies showed that fluid biomarker levels rise during ATT treatment gaps, indicating that continued dosing may be the best approach to control amyloid levels.
- Appropriate use criteria for donanemab are aligned with those for lecanemab:
  - Caution is emphasized when it comes to use in those on anticoagulants.
  - Clinician judgement remains paramount in individual cases.
- The trial of a transferrin-based brain shuttle mechanism showed reduced ARIA rates and rapid amyloid clearance, suggesting potential for safer ATTs.
- Collaboration and post-hoc analysis are vital to understand safety risks and optimal dosing regimens.

Amyloid-related imaging abnormalities (ARIA)



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Much of the longer-term and real-world data focused on ARIA prevalence, prediction, and management. Dosing adjustments were found to be highly successful in lowering ARIA risk and a new ultrafast MRI technique provides promise for more efficient monitoring of ARIA.

Expert insights

- Observations show real-world ARIA rates aligning closely with trial data, reinforcing confidence in the safety profile of ATTs outside of clinical trials.
  - Education on ARIA needs to extend to ER and stroke physicians to avoid mismanagement and serious consequences.
- Development of MRI protocols focused solely on ARIA detection could reduce scan time, improving cost-effectiveness and accessibility of regular monitoring.
- Studies are ongoing to identify additional biomarkers (beyond APOE e4) for predicting ARIA risk, aiming to enhance patient safety by refining risk stratification.
- AI has the potential to predict individual ARIA risks and monitor adverse events, enhancing both safety and personalized care strategies.
  - Natural Language Processing (NLP) applications in AI are streamlining adverse event reporting, potentially capturing a more accurate safety profile.
- Future efforts should prioritize clear communication of risk to patients and equipping clinicians with resources to effectively discuss treatment implications and safety management.

Summary

CTAD 2024 provided helpful updates on the use of blood-based biomarkers and ATTs in clinical practice, showing overall optimistic results on their utility in a variety of patient subgroups. The key theme was around increasing the safe integration of the disease modifying therapies and ensuring the correct patients are receiving them as early as possible.

Timely diagnosis in all populations

Underrepresentation of minority groups, particularly Black and Hispanic populations, in clinical trials for Alzheimer's disease remains an issue which can in turn impact timely and accurate diagnosis in clinical practice. Blood-based biomarker tests have the potential to address this issue, but further research is needed.

Blood-based biomarker utility in clinical practice

Blood tests show strong concordance with PET and CSF results across various subgroups and clinical settings, suggesting they could streamline Alzheimer's diagnosis. Understanding how comorbidities and other patient factors may affect results is an ongoing research effort.

Real-world use of ATTs

Real-world data show that ATTs are being used safely and effectively, though only about 10% of patients are eligible due to later-stage diagnosis, comorbidities, or personal choice. Understanding around the optimal dosing in terms of safety and amyloid clearance is rapidly emerging but more research and real-world data is required to further define ATT contraindications.

Enhancing patient safety

Real-world ARIA rates for those treated with ATTs match trial data, supporting their safety profile. However, to prevent mismanagement, education on ARIA needs to reach the wider multidisciplinary team. Innovations in MRI approaches and the use of AI could reduce resource and cost whilst enhancing patient safety.

More resources

Read our **News Nuggets**

Detailed summaries of the data presented at CTAD.

Watch and listen to our **Breakfast Bites**

On-site interviews with delegates from CTAD share their insights on the data and topics presented.

Take-away our **Microdigests**

Summary of key developments presented at CTAD in downloadable infographics.

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