Latest Discoveries in Alzheimer's Disease

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Alzheimer Disease: A Global Epidemic

Alzheimer Disease: Major Cause of Mortality

Amyloid and Tau Cascades in Alzheimer Disease
Other Disease Mechanisms and Pathways

Stages of Neurodegeneration

The pathological evolution of Alzheimer’s disease

AD Biomarker Profile: High CSF tau and p-tau181 and low CSF Aβ42


Leuzy et al. Brain. 2016 Sep;139(9):2540–2553 (with permission—Open Access)

CSF tau/Aβ42 and p-tau181/Aβ42 detect preclinical AD

I. UPDATED RESEARCH FRAMEWORK FOR AD
TOWARDS BIOMARKER-BASED DEFINITIONS OF AD

Theoretical Model of Disease Progression

Biomarkers: Central Concept in the Updated Research Framework of AD: AT(N)
The ATN Framework for Alzheimer Disease Diagnosis and Characterization

Amyloid “A”  Tau “T”

Imaging Biomarkers of Neurodegeneration “N”

Volumetric MRI  FDG-PET

No atrophy  Atrophy  Normal metabolism  AD pattern of hypometabolism

Advances in AD Diagnosis:

Blood Biomarkers and Emerging Markers of Other Pathologies

CSF p-tau217 outperforms CSF p-tau181
Plasma p-tau181: New AD-Specific Blood Marker

Plasma p-tau217: Great Promise as Most Sensitive and Specific Blood Test for AD

Plasma Markers Can Detect Brain Amyloid

P-tau231 May Precede Amyloid in AD Brains
Understanding the Clinicopathological and Molecular Heterogeneity of AD

New Biomarkers And Big Data Analytics: Data-Driven Disease Models

AI Algorithms Identify 4 AD Subtypes
Update on Investigational AD Therapies

NEWS: Aducanumab FDA-Approved June 7, 2021 As First Disease-Modifying Treatments for AD

- Aducanumab is an amyloid beta-directed antibody indicated for the treatment of early symptomatic Alzheimer’s disease.
- This targets soluble and insoluble (aggregated) Aβ peptides
- This indication was just recently approved under accelerated approval based on reduction in amyloid beta plaques observed in treated patients.
- Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- Both Phase 3 clinical trials includes patients with:
  - Clinical Dementia Rating (CDR) score of 0.5 (equivalent to MCI)
  - MMSE 24-30
  - RBANS (Repeatable Battery for Assessment of Neuropsychological Status) delayed memory index of ≤ 85

Aducanumab reduces amyloid burden

**Results**

**Anti-amyloid immunotherapies: Effectively Remove Amyloid And May Slow Down Disease Progression**

![Images and diagrams related to the text content]
Clinical Endpoints

Clinical Endpoints-Continued

Biomarker End-points

Aducanumab –in the clinic

- Is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.
- Patients with mild cognitive impairment due to Alzheimer disease
- Evidence of Amyloid on Amyloid-PET scans
- Brain MRI within a year prior to starting the infusion as a baseline
- Safety has not been assessed in patients who have pre-treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation
ARIA-E and ARIA-H

- ARIA-E or ARIA-H were observed in 41% of treatment compared to 10% of placebo groups
- ARIA-E was observed in 35% of treated patients compared to 3% of placebo
- ARIA-E was more common in APOE4 carriers (42%) vs APOE4 noncarriers (20%)
- Most ARIAs occurred within the first 8 doses but can occur any time
- ARIAs were mild in 30%, moderate in 58% and severe in 13%
- Resolution occurred in 68% of ARIA-E patients by 12 weeks, 98% overall after detection
- 10% of patients on the full dose had more than one episode of ARIA
- Besides ARIA, angioedema and hypersensitivity have been reported

Amyloid Related Imaging Abnormalities (ARIs)

Table 2: ARIA MRI Classification Criteria

<table>
<thead>
<tr>
<th>ARIA Type</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>ARIA-E</td>
<td>FLAIR hypointensity confined to subcortical white matter involving one side, white matter involvement &lt; 5 cm</td>
<td>FLAIR hypointensity &gt; 25%, with significant subcortical white matter involvement</td>
</tr>
<tr>
<td>ARIA-H</td>
<td>1 or more new microhemorrhages</td>
<td>1 or more new microhemorrhages</td>
</tr>
<tr>
<td>ARIA-H superficial edema</td>
<td>1 focal area of superficial edema</td>
<td>1 or more new areas of superficial edema</td>
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ARIA Follow-up

- Enhanced clinical vigilance for ARIA is recommended during the first 8 doses
- Clinical evaluation of symptomatic patients with suspected ARIA should include a brain MRI
- Brain MRIs should be obtained routinely prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) to evaluate for the presence of asymptomatic ARIA.
- For patients with radiographic ARIA, enhanced clinical vigilance is recommended including possible need for additional MRIs
- For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule.
- In Studies 1 and 2, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H.
- In Studies 1 and 2, permanent discontinuation of dosing was required for radiographically severe ARIA-H.
Unraveling New Disease Mechanisms

Beyond Protein Aggregation:
Immune Mechanisms and Vascular Disturbances are Key Players
Targeting Inflammation in AD; Anti-TREM2 Antibodies

Image by Gerry Shaw. [ImemediaCommons]
Schelpckow et al. EMBO Mol Med 12:e11227

RNA-seq identifies different microglial subtypes in AD

Novel Therapeutic Targets
Big Data Analytics at Forefront of AD Drug Discovery

VGF Gene As A Key Regulator of AD

Beckman et al. Nat Commun 11, 3942 (2020) with permission
AD and the Gut Microbiome