Alzheimer's biomarkers and its use in drug development

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ABSTRACT

- Alzheimer's disease (AD) is a common, irreversible subtype of dementia in industrialized countries and characterized by the progressive appearance of abnormalities in biomarkers before its symptoms.
- Pre-clinical diagnosis is the key to a better efficiency in treatments when administrated.
- However, biomarkers have shown a more important role in subject stratification rather than the identification of subjects prone to develop AD.
- A future standardization of these to enhance clinical essays and the development of new drugs is considered a medical need.

CURRENT TREATMENT

Cholinesterase Inhibitors [3]

- Donezepile
- Rivastagmine
- Galantamine

NMDA-R antagonist [3]

- Memantine

Therapeutic designs have failed → **Lack of connection between AD pathways** → **Biomarkers** gained importance in defining MCI: new therapeutic window

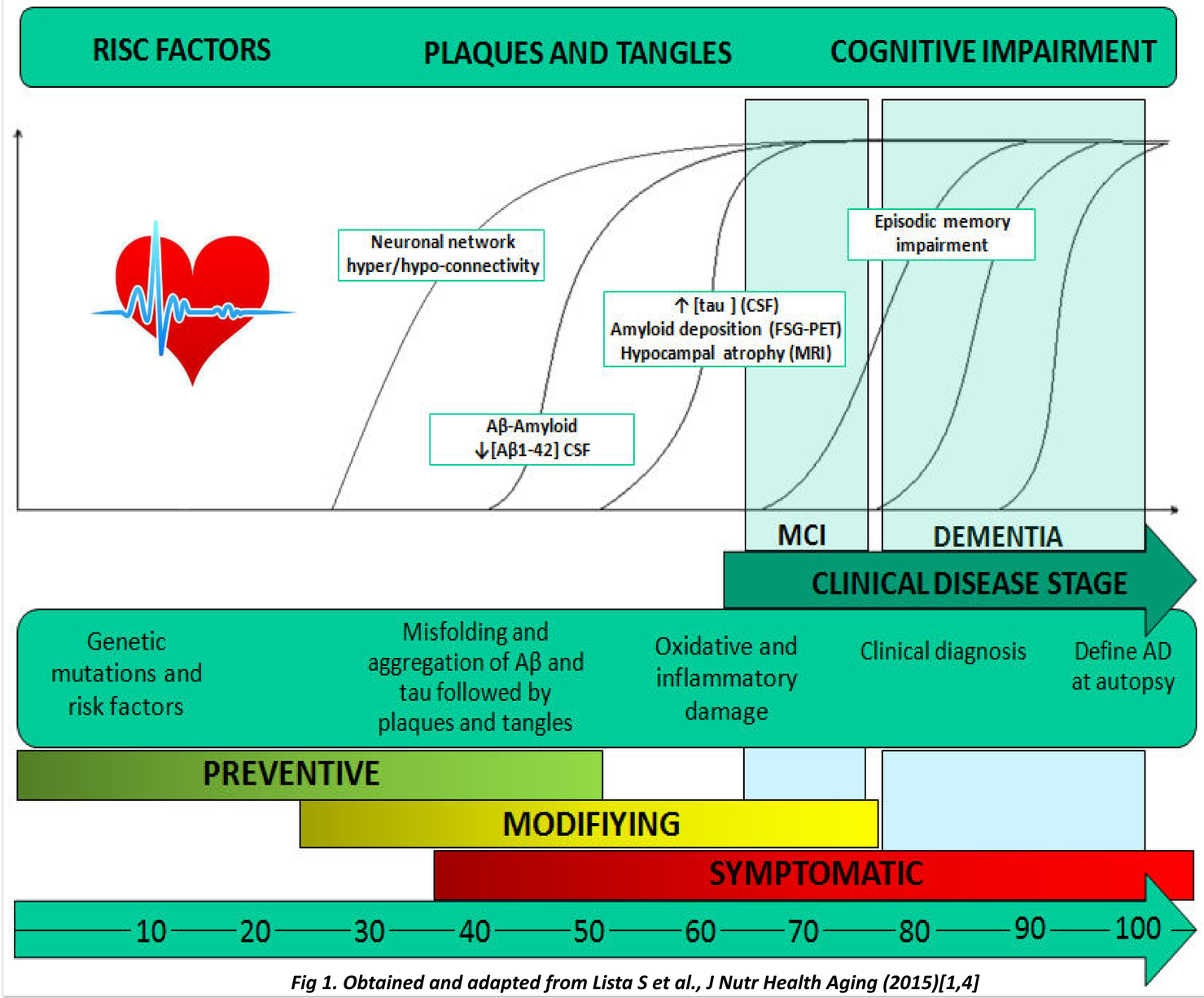

Fig 1. Obtained and adapted from Lista S et al., J Nutr Health Aging (2015)[1,4]

CSF

[$A\beta_{1-42}$] [t-tau] [p-tau]

FDG-PET

Amyloid fibrils deposition

MRI

Regional atrophy

MAIN ROLE OF BIOMARKER PROFILES

- Defining populations
- Confirming target access
- Identifying AD at earlier stages and reflecting pathogenic process
- Assessment of treatment effects and clinical status improvement

DRUGS AGAINST AMYLOID DEPOSITION

Anti-Amyloid Agreggant Agents[3]

- Tramiprosat (Phase III) (-)
- Colostrinina (Phase II) (±)
- Scyllo-Inositol (Phase II) (±)

Chelants

- PTB2 (Phase IIa) (+)

γ-secretase inhibitors

- Semagacestat (Phase III) (-)
- Tarenflurbil (Phase II) (-)
- Avagacestat (Phase II) (-)

β-secretase inhibitors

- CST-21166 (Phase I) (+)

α-secretase inhibitors

- Etazolate (Phase IIa) (+)

PASSIVE IMMUNE THERAPY: MONOCLONAL ANTIBODIES

Randomized, multicenter,double-blind, placebo-controlled Phase III (-) trials (2014)[2]

- Mild-to-moderate subjects, targetting Aβ.

BAPINEUZUMAB	SOLANEZUMAB

• Target → N_t
• Phase II:
  • Not improve cognition or function significantly + vasogenic edema
  • ↓ fibrilar Aβ accumulation (PET)
• **Apoε4 -** : ↓ ARIA-E + apparent treatment effect
	• Target → epitope in the middle
	• Phase III:
	• Targeting Aβ has a positive effect on cognition (although no biomarker changes for treatment effect)
	• ↓ cognitive decline stable for 80 weeks
	• ↑ in total CSF and ↓CSF levels Aβ1-40

What we have learned about Phase III trails? [2]

- Value of stratifying participants
- Biomarker and structural neuroimaging studies in Aβ - subjects are needed
- Amyloid removal alone may not be sufficient to slow AD progression
- Targeted trials are useful in AD, but new approaches are needed
- Phase II should be larger to a more definitive clinical efficacy signal

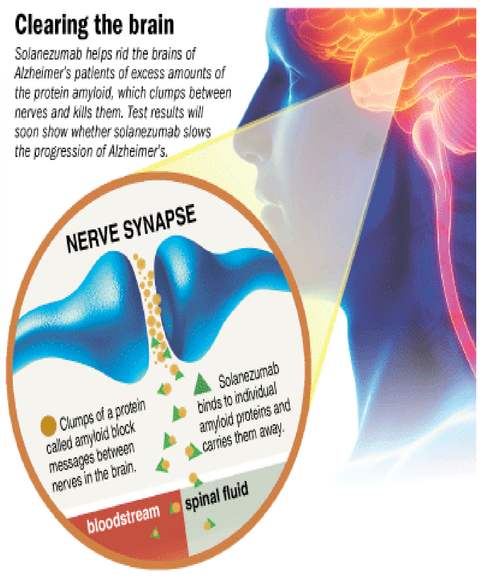

Fig 2. Effect of Solanezumab in human brain

DISCUSSION

- Therapeutic trials should be focused on early stages, requiring more diagnosis tools. New diagnostic criteria based on biomarkers has provided a new therapeutic window for detection in early stages.
- Even though amyloid positivity is a good marker on identifying subjects, actual studies with PET and CSF are difficult to standardize globally. So new positivity measures are needed.
- Evidence of target engagement in SNC and evidence of downstream effects on relevant biomarkers may be established,
- As a result of Phase III trials failure, new trial designs, including adaptive and targeted designs, should be explored.

REFERENCES

1. Lista, S. et al.,(2015). Paths to Alzheimer's disease prevention: From modifiable risk factors to biomarker enrichment strategies. *The journal of nutrition, health & aging*, 1-10.
2. Vellas, B. et al.,(2013). Designing drug trials for Alzheimer's disease: what we have learned from the release of the phase III antibody trials: a report from the EU/US/CTAD Task Force. *Alzheimer's & Dementia*, *9*(4), 438-444.
3. Konstantina G. et al.,(2013) Current and future treatments for Alzheimer's disease. *Therapeutic Advances in Neurological Disorders* 6(1): 19–33.
4. Prestia, A. et al., (2015). Prediction of AD dementia by biomarkers following the NIA-AA and IWG diagnostic criteria in MCI patients from three European memory clinics. *Alzheimer's & Dementia*.

(+) Promising results, (-) Disappointing results (±) Doubtful results / N_t: N-terminal / CSF: cerebrospinal fluid / Aβ : Amyloid- β/ FDG-PET: Fludeoxydeglucose- Positron Emission Tomography / MCI: Magnetic Ressonance Imaging/ ARIA-E: Amyloid-Related Imaging Abnormalities-Edema/ Apoε4: Apolipoprotein ε4 allele