EU regulatory perspective on the potential use of biomarkers in AD drug development

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Agenzia Italiana del Farmaco
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Public Declaration of transparency/interests*

Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator				X	
Individual's Institution/Organisation receives a grant or other funding	X				
CME Courses	X				

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Note: For this presentation I am not receiving any compensation

Why is AD a regulatory challenge?

- Animal models do not reflect human pathophisiology of the disease
- Diagnosis can be formulated in vivo with less probability in early stages
- Trial design is not optimized to detect significant changes in milder patients
- Biomarkers change role in the different phases of development
- Disease modification definition relies on uncertain biological evidence

Biomarkers in drug development

- Target engagement
- Proof of mechanism
- Proof of concept
- Enrichment
- Diagnosis (supportive or mandatory)
- Outcome (supportive)
- Outcome (disease modification)

Target engagement/proof of mechanism

>>>The value and qualification of several biomarkers has been improved considerably and some of them may be used as primary endpoint in proof of mechanism/principle studies >>>

- Agents directly targeting Aβ deposition by active and passive immunization
  - ↑ Plasma and CSF Aβ species
  - ↓ Amyloid load at PET
- Agents targeting Aβ accumulation via inhibition or modulation of the γ-secretase APP cleaving enzyme and β-secretase cleavage enzyme BACE1
  - ↓ Plasma and CSF levels of Aβ42, Aβ40, sAPPβ (dose-dependent)

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ORIGINAL PAPER

Do current therapeutic anti-Aβ antibodies for Alzheimer's disease engage the target?

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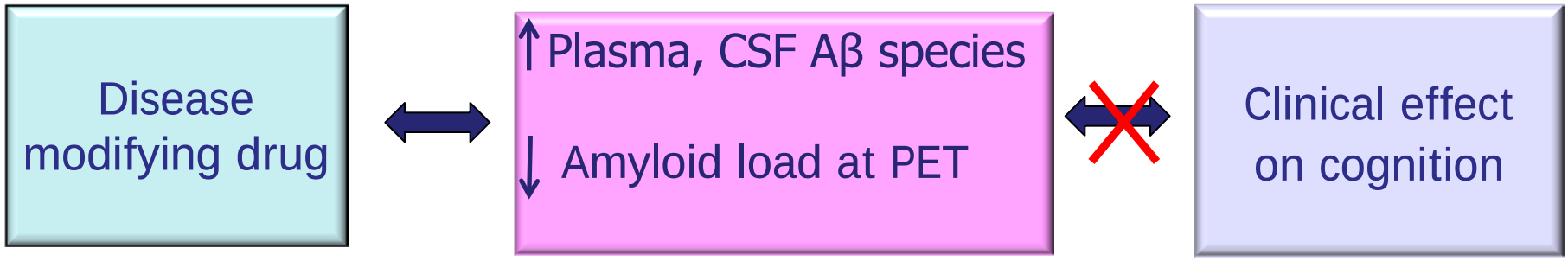
Abstract Reducing amyloid-β peptide (Aβ) burden at the pre-symptomatic stages of Alzheimer's disease (AD) is currently the advocated clinical strategy for treating this disease. The most developed method for targeting Aβ is the use of monoclonal antibodies including bapineuzumab, solanezumab and crenezumab. We have synthesized these antibodies and used surface plasmon resonance (SPR) and mass spectrometry to characterize and compare the ability of these antibodies to target Aβ in transgenic mouse tissue as well as human AD tissue. SPR analysis showed that the antibodies were able to bind Aβ with high affinity. All of the antibodies were able to bind Aβ in mouse tissue. However, significant differences were observed in human brain tissue. While bapineuzumab was able to capture a variety of N-terminally truncated Aβ species, the Aβ detected using solanezumab was barely above detection limits while crenezumab did not detect any Aβ. None of the antibodies were able to detect any Aβ species in human blood. Immunoprecipitation experiments using plasma from AD subjects showed that both solanezumab and crenezumab have extensive cross-reactivity with non-Aβ related proteins. Bapineuzumab demonstrated target engagement with brain Aβ, consistent with published clinical data. Solanezumab and crenezumab did not, most likely as a result of a lack of specificity due to cross-reactivity with other proteins

K. J. Barnham and L. A. Miles contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00401-014-1290-2) contains supplementary material, which is available to authorized users.

From target engagement to proof of concept



Why did anti-amyloid therapies failed to demonstrate POC in clinical setting?

- Validity of the amyloid hypothesis
- Treatments started too late
- Flaws in the mechamism of action of individual agents (ability to cross the BBB or to capture different human amyloid species or even target engagement)

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Biomarkers for Enrichment

Qualification opinion (public document)

- ✓ Hippocampal volume (atrophy) by MRI
- ✓ CSF Aβ 1-42 **and** t-tau
- ✓ PET amyloid imaging (positive/negative)

CSF and PET biomarkers are interchangeable for the purpose of enrichment

Qualification advice (confidential)

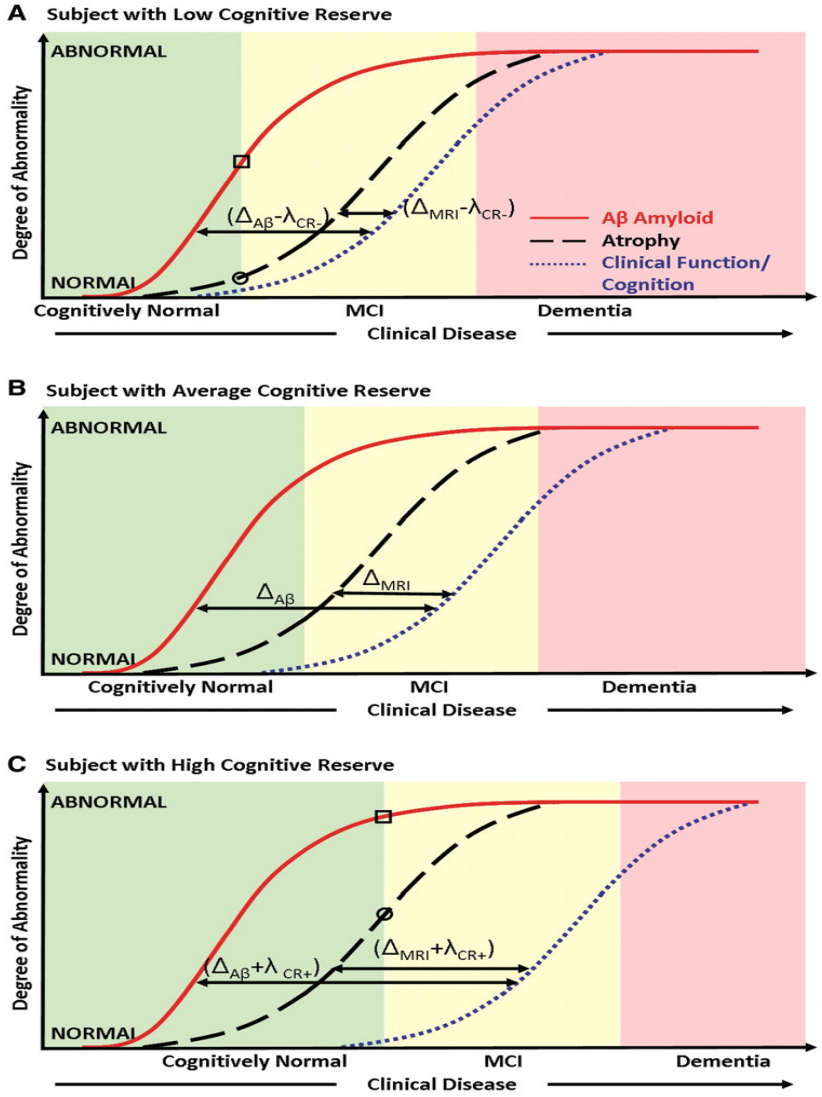
- ✓ Validation of CSF assays for Aβ42
- ✓ CSF assays cut off determination

Aβ42 alone has a lower sensitivity and specificity and can only be used for enrichment for research purpose. Can results be generalized to clinical population?

Diagnosis of Prodromal AD/MCI/MND

IGW	NIA-AA	DSM5
Objective memory impairment	Objective or subjective memory impairment	Subjective and objective cognitive decline
No functional impairment not even in iADL	Accept minor problems in performing iADL.	No functional impairment but increased compensatory strategies
Positive biomarker (amyloid PET of CSF Aβ1-42 and Tau)	Positive biomarker supportive but not mandatory	No need for biomarker

Diagnosis: from a clinical to a biological entity



Depending on individual cognitive reserve, the same type of patient with the same levels of biomarker would or would not display clinical symptoms

- When shall we start treatment?
- Can prodromal AD and mild AD populations be combined?

Diagnosis of Preclinical AD

EOAD

✓Etiology is genetic and mutations have been characterized (APP, PSEN1, PSEN2)

✓Secondary prevention trials are ongoing

✓Symptomatology overlaps with LOAD

What can be extrapolated into LOAD??

LOAD

✓Etiology is multifactorial

✓Diagnosis relies solely on the presence of pathopysiological biomarkers

(↓ Aβ 1-42 **and** t-tau; ↑ Amyloid retention at PET)

✓Symptomatology overlaps with EOAD

How can other factors influencing progression (e.g. lifestyle, metabolic) be controlled?

Factors influencing biomarker positivity

IC-P-025

AGE IS A SIGNIFICANT FACTOR IN DETERMINING PATHOLOGICAL POSITIVITY MEASURED WITH [18F]FLORBETAPIR PET

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Research Article

Insulin resistance predicts brain amyloid deposition in late middle-aged adults

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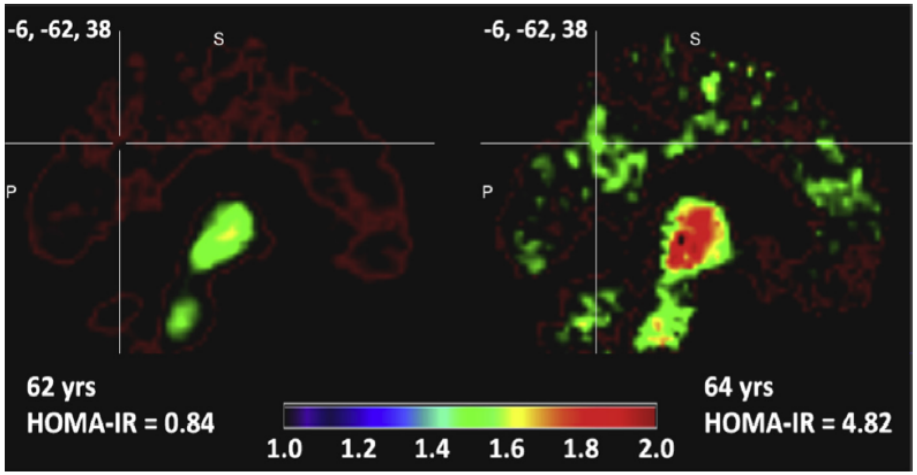

Fig. 2. Pittsburgh compound B (PiB) images and insulin resistance. Amyloid uptake images in age- and sex-matched representative participants, who varied by the homeostatic model assessment of insulin resistance (HOMA-IR). Two representative sagittal PiB images are shown for a participant with low IR (HOMA-IR <2) or high IR (HOMA-IR ≥ 2). The color bar depicts the PiB distribution volume ratio (DVR), a quantitative index of PiB uptake.

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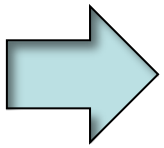
Biomarkers as outcome

- Reduced Hippocampal volume (MRI)
- Decreased CSF Total Tau
- Reduced cortical amyloid load in the brain as measured by PET imaging
- Tau PET technique for longitudinal evaluation of tau deposition.
- FDG PET



- Not prospectively qualified as outcome measure.
- The trajectory of change of different biomarkers may vary over time
- Supportive evidence may arise from changes in one biomarker and not another

How should biomarker data be interpreted?

Disease modification definition (2 steps)

1) Improvement in the rate of decline (cognition and function)

2) Evidence of biomarker change

This definition relies on uncertain biomarker evidence.

In other neurodegenerative disorders biological defects translate into heterogeneous clinical manifestation

Clinical meaningful benefit is the ultimate goal of dementia therapy

Alternative trial design approaches (delayed start or withdrawal) or alternative analyses (time to event/slope analysis) are encouraged to demonstrate clinical benefit even in absence of biomarker data.

Questions

- Can biomarker data be extrapolated from studies in EOAD?
- What is needed to standardize biomarker requirements for diagnosis of Prodromal AD across the different sets of criteria?
- Preclinical states of AD, in absence of a genetic mutation, are defined as “asymptomatic at risk” if there is positive evidence of either amyloid retention at PET or CSF Aβ and Tau biomarkers. Can this be considered a clinical population?
- How should biomarker evidence be interpreted in the context of a disease modifying claim?