I «disease-modifying drugs» nello stato preclinico dell’AD: quali evidenze?

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DEFICIT COLINERGICO

Figure 2. Functional features of the cholinergic system. ACh=acetylcholine; AChE=acetylcholinesterase; BuChE=butyrylcholinesterase; ChAT=choline acetyltransferase; CoA = coenzyme A.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Cholinesterase inhibition</th>
<th>Medical Authority Approval</th>
<th>Dosing</th>
<th>AD Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrine</td>
<td>Cognex</td>
<td>Not used due to hepatotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>Cholinesterase inhibition</td>
<td>FDA: 1996, EMEA: 1997; QD dosing; for mild, mod, severe AD</td>
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<tr>
<td></td>
<td>Memac</td>
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<tr>
<td>Rivastigmine</td>
<td>Exelon</td>
<td>Cholinesterase inhibition</td>
<td>BID; patch formulation released; for mild to mod AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prometax</td>
<td>Butyrylcholinesterase inhibition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne</td>
<td>Cholinesterase inhibition</td>
<td>BID; XR formulation released; for mild to mod AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reminyl</td>
<td>Nicotinic receptor modulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda,</td>
<td>Glutamate receptor modulation</td>
<td>Approved 2003; for moderate to severe AD</td>
<td></td>
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<tr>
<td></td>
<td>Ebixa</td>
<td></td>
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</tbody>
</table>
GLOBAL RESPONDERS to ChEIs

<table>
<thead>
<tr>
<th>Study</th>
<th>ChEI</th>
<th>ChEI responder</th>
<th>Placebo responder</th>
<th>Total subj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers 1998</td>
<td>Donepezil</td>
<td>107/305</td>
<td>27/150</td>
<td>455</td>
</tr>
<tr>
<td>Rogers 1998b</td>
<td>Donepezil</td>
<td>76/298</td>
<td>17/152</td>
<td>450</td>
</tr>
<tr>
<td>Burns 1999</td>
<td>Donepezil</td>
<td>125/544</td>
<td>38/274</td>
<td>818</td>
</tr>
<tr>
<td>Rosler 1999</td>
<td>Rivastigmine</td>
<td>149/467</td>
<td>44/220</td>
<td>687</td>
</tr>
<tr>
<td>Raskind 2000</td>
<td>Galantamine</td>
<td>64/357</td>
<td>27/196</td>
<td>553</td>
</tr>
<tr>
<td>Wilcock 2000</td>
<td>Galantamine</td>
<td>84/414</td>
<td>33/203</td>
<td>617</td>
</tr>
<tr>
<td>Rockwood 2001</td>
<td>Galantamine</td>
<td>61/240</td>
<td>24/123</td>
<td>363</td>
</tr>
<tr>
<td>Wilkinson 2001</td>
<td>Galantamine</td>
<td>59/179</td>
<td>23/83</td>
<td>262</td>
</tr>
</tbody>
</table>

Favours ChEI

Favours placebo

Meta-analytic difference

30% 20% 10% 0% -10%

Responders: improvement or better (excluded unchanged) on a global assessment scale (type 1)

Lanctot et al., 2003
Donepezil | Aricept | Cholinesterase Inhibition | FDA: 1996, EMEA: 1997; QD dosing; for mild, mod, severe AD
Rivastigmine | Exelon | Cholinesterase Inhibition | BID; patch formulation released; for mild to mod AD
Galantamine | Reminyl | Cholinesterase Inhibition | BID; XR formulation released; for mild to mod AD

- **all three** ChEIs have demonstrated **efficacy** for mild to severe AD
- improvement is **statistically significant** but **clinically marginal**
- a trial for most patients is recommended (**Grade 1A**) 
- direct comparisons do **not suggest differences** (**Grade 2B**)
Disease-modifying treatments
AD pathogenesis: the amyloid cascade hypothesis
AD: disease-modifying strategies

1. Anti-amyloid production and aggregation agents:
   . γ-secretase inhibition
   . BACE-1 inhibition

2. Amyloid removal: immunotherapy

3. Anti-tau protein compounds

Golde et al, 2010
From the first preclinical evidence of effectiveness of vaccination against Aβ in mice...

**Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse**


*Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA*

*Nature, 1999*

to the development of many disease-modifying drugs....
Active immunization
HUMAN TRIAL: AN1792 + AS21 adjuvant

- **phase IIa** study
- 372 probable AD (mild to moderate)

**Study discontinuation!**

Aseptic meningoencephalitis in 18 of 300 (6%) immunized patients

By the time of discontinuation:
- 24 patients received 3 immunizations
- 274 received 2 immunizations
Results after 6 yrs: clearance of amyloid plaques, but no evidence of increased survival and no improvement in the time to severe dementia!
New approach: passive immunization
2016: state of the art

- 2003: AN 1792 → failed due to adverse events
- 2012: Bapineuzumab → failed to reach primary endpoints (Salloway et al., 2014)
- 2014: Gantenerumab → withdrawn in Dec 2014
- 2014: i.v. Ig → failed (Dodel et al., 2013)
- 2014: Solanezumab in moderate AD: failed (Doody et al., 2014)

- semagacestat
- avagacestat \( \gamma \)-secretase inhibitors → failed
  
  Doody et al., 2013, Coric et al., 2012

- CAD 106 → phase II complete
- Solanezumab → phase III: positive results only in mild AD
- MK-8931 → BACE inhibitor, phase II
- Aducanumab → phase Ib completed
The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease


Decreased amyloid load on PiB-PET

11C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer’s disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Lanace Neurol 2010; 9: 363-72
Why did so many trials fail?

Population recruited:

- patients may not have AD but other dementias instead

- too late treatment (removal of plaques is not sufficient to halt the disease progression) \(\rightarrow\) treat preclinical/prodromal AD
Pre–dementia phase

Use of biomarkers to **enrich** the cohort studied with subjects with an ongoing **AD pathology**

“MCI” with a positive biomarker

“Prodromal AD” *(Dubois et al., 2010)*
Clinical diagnosis of Alzheimer’s disease:
Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

NINCDS-ADRDA 1984

Time line AD criteria
- MRI
- fdgPET
- CSF
- mutation
The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease


Biomarkers of underlying pathology: CSF (amyloid and tau) - PET with amyloid (and tau) tracers - mutation

Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galaska, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

Time line AD criteria

NINCS-ADRDA 1984

NIA-AA 2011

IWG-2 2014
Which biomarker?

Reflecting Aβ deposition:
- CSF low Aβ
- PET Aβ tracers (PiB, Fluorbetapir, Fluorbetaben, ecc)
- presence of a known causal mutation (APP, PSEN 1 and 2)

Reflecting tau deposition:
- CSF high tau
- PET tau tracers ([¹⁸F]AV-1451)

Attempts to select cohort have been done so far targeting Aβ, on the basis of the «amyloid hypothesis»

**BUT**

Aβ accumulation does not correlate well with extent of neuronal loss or cognitive dysfunction
Cerebrospinal Fluid Levels of β-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia

Amyloid CSF levels: changed 10 years before symptoms appearance

Tau CSF levels: changed 5 years before symptoms appearance
Use of BMs in clinical trials

**Ideally:** treat subjects with low CSF Aβ but normal tau (no cell death yet) → **prevent** all pathogenic mechanisms related to Aβ deposition, responsible for neurodegeneration.

**In practice:** considering the duration of a trial (2-3 years) and the lack of outcome measures in asymptomatics or surrogate biomarkers for progression → **treat** «**MCI due to AD**» (outcome measure: conversion from MCI to AD)

*Sperling et al., 2014*
PET TAU tracers: $[^{18}F]{AV-1451}$

The pattern of increased $[^{18}F]{AV-1451}$ retention highly overlapped with regions that showed decreased $[^{18}F]{FDG}$ uptake → hypometabolism and symptomatology are more closely linked to tau than to Aβ
PRE-MCI: AD trajectory

Stage 0
No biomarker abnormalities

Stage 1
Asymptomatic amyloidosis
- High PET amyloid retention
- Low CSF Aβ1-42

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

SNAP
Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

Aβ
asymptomatic
Aβ+Tau

MCI ➔ Dementia due to AD

Sterling et al., 2014
Stage 0: primary prevention

- About 40-50% of people
- Cardiovascular risk factors
- Mediterranean diet
- Physical activity

Sterling et al., 2014; Jack et al., 2011, mod.
Nature and nurture: the case of Romania

Cornutiu et al, 2011
Monkeys as models for AD

- Express Aβ

- With aging: **develop senile plaques**, although to a lesser extent as compared with humans, but **no NFTs**

- High amount of senile plaques and NFTs in an **obese** monkey

*Bufill et al., 2013*
Stage 1: secondary prevention

Stage 1 (10-15%): secondary prevention with a treatment interfering with Aβ deposition

Immunization: from treatment for symptomatics to prevention in asymptomatics

Sterling et al., 2014
Cognitive trajectory in normal aging and AD

Sterling et al., 2014
Stopping Alzheimer’s Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms.

GREG MILLER  17 AUGUST 2012  VOL 337  SCIENCE

Alzheimer’s Prevention Trials at a Glance

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Treatment</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>API: Alzheimer’s Prevention</td>
<td>300 members of Colombian families, including 100 carriers of a mutated PSEN1</td>
<td>Crenezumab (Genentech)</td>
<td>Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy</td>
</tr>
<tr>
<td>Initiative</td>
<td>gene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIAN: Dominantly Inherited</td>
<td>240 members of families with early-onset Alzheimer’s; 60 have a mutation in one of three genes</td>
<td>Three anti-amyloid therapies to be determined</td>
<td>An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects</td>
</tr>
<tr>
<td>Alzheimer Network</td>
<td></td>
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</tr>
<tr>
<td>A4: Anti-Amyloid Treatment of</td>
<td>1500 healthy seniors, including 500 with amyloid-positive brain scans</td>
<td>One anti-amyloid therapy to be determined</td>
<td>Primary: Cognitive. Secondary: Biomarkers</td>
</tr>
<tr>
<td>Asymptomatic Alzheimer’s</td>
<td></td>
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</tr>
</tbody>
</table>
Alzheimer Prevention Initiative (API)
- Phase II: **Crenezumab** tested in a large Colombian *PSEN1* cohort

Dominantly Inherited Alzheimer Network (DIAN)
- Phase II: **Solanezumab** vs gantenerumab in carriers of mutations in *APP, PSEN1* and *PSEN2*

Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease (A4)
- Phase III: **Solanezumab** vs placebo in cognitively normal people (65-85 years) with evidence of Aβ accumulation
Additional vaccines waiting for clinical trials

- **ACI-24** (AC Immune): Ab1-15 peptide to which on both ends two lysines were attached. Antigen embedded in a liposome membrane. Currently evaluated in a phase I/II clinical trial in Denmark, Finland and Sweden.

- **Affitope AD-02** (Affiris, Vienna AT and licensee GSK Biol.): is 6-aminoacid peptide vaccine targeting the N-terminus of Aβ. European phase II clinical trial in 420 patients ongoing.

- **Affitope-AD-03** (Affiris and licensee GSK Biol.): phase I completed in 2011, results not yet published.

- **ACC-001** (vanutide cridificar; Pfizer). Two Phase II studies in patients with mild to moderate AD: one in Japan (completed) and one ongoing in USA.

- **UB-311** (United Biomedical): intramuscularly administered vaccine targeting N-terminal amino acids 1-14 of Aβ in phase I clinical trials in Taiwan in patients with mild to moderate AD.

- **V-950** (Merck): Phase II, double-blind, randomized, placebo-controlled, dose escalating study completed, but results not yet published.

*D. Galimberti, E. Scarpini, J. Neurol Sci, 2013*
Additional monoclonal antibodies waiting for clinical trials

• **PF-04360365** (Pfizer, phase II completed)

• **GSK933776A** (GlaxoSmithKline, phase I completed)

• **NI-101** (Biogen Idec, phase I clinical trial in patients with mild to moderate AD ongoing)

• **PF-05236812** (Janssen Alzheimer Immunotherapy and Pfizer, phase I trial ongoing)

• **RN6G** (Rinat Neuroscience Corp., New York, now Pfizer, phase I completed)

• **SAR-228810** (Sanofi, phase I ongoing)

• **BAN-2401** (Eisai, phase I trial in 80 patients with mild to moderate AD ongoing).

*D. Galimberti, E. Scarpini, J. Neurol. Sci., 2013*
Short Research Communication

Transgenic Rice Expressing Amyloid β-peptide for Oral Immunization

Taiji Yoshida, Eiichi Kimura, Setsuo Koike, Jun Nojima, Eugene Futai, Noboru Sasagawa, Yuichiro Watanabe, and Shoichi Ishiura

The future: vaccination as primary prevention
Stages 2-3: acting on tau

Strategies (preclinical):

- **Inhibition of GSK3β**: (kinase phosphorylating tau)
- **Activation of phosphatases** (PP2A)
- **Vaccination**: (more difficult as tau is intracellular)
Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer’s disease

Ludovic Collin, Bernd Bohrmann, Ulrich Göpfert, Kristzina Oroszlan-Szovik and Laurence Ozmen.

1 Roche Pharmaceutical Research and Early Development, Neuroscience Ophthalmology and Rare Diseases Discovery & Translational Area, Roche Innovation Center Basel, Grenzacherstrasse 124, CH-4070 Basel, Switzerland
2 Roche Pharmaceutical Research and Early Development, Large Molecule Research, Roche Innovation Center Penzberg, Nonnenwald 2, D-82377 Penzberg, Germany

- Triple transgenic mouse model of AD
- Anti-tau/pS422 anti-body binds to membrane-associated tau/pS422 and antigen-antibody complexes are cleared intracellularly.
- Chronic, peripheral administration of anti-tau/pS422 antibody reduces the accumulation of tau pathology.
Stages 2-3: acting on tau

- Inhibition of GSK3β* (kinase phosphorylating tau)
- Activation of phosphatases (PP2A)
- Vaccination° (more difficult as tau is intracellular)

- Methylene blue (Rember), Phase II - ongoing
- *Tideglusib, Phase II – failed
- ° AADvac1, Phase I, ongoing but not recruiting
Conclusions: open questions for early intervention

- Are subjects in early intervention trials *early enough in disease process to respond* to interventions?

- **How early is early enough?**
  - What are the key variables that determines when a subject responds to a disease modifying drug, such as an anti amyloid agent?
    - Cognitive impairment?
    - Neurodegeneration?
    - Tau or Aβ levels?

- **Are earlier trials feasible?**
  - Prodromal AD trials are hard to enroll
  - Earlier stages of illness: TBD (use of BMs? Feasibility?)

- **What is optimal design of early intervention trials**
  - duration (more than 2-3 years)?
  - costs
  - ethical issues
Active immunotherapy: CAD106

- New antigen designed to generate high Aβ antibody titers without inducing Ab-reactive T-cells
  - Abeta 1-6 peptide, shorter than known human T-cell epitopes
  - Its sequence is predicted not to activate T-cell responses
  - Experimentally it contains B-cell but not T-cell epitopes

Reduction of amyloid accumulation

- Amyloid plaque area: ~80% lower than in control mice
- Longer treatment and start at earlier age: increased effect!

**Staufenbier, M. et al., Abst O1-06-01- ICAD 2006 Madrid**
Immunization of Rhesus Monkeys

CAD106-induced Aβ antibodies:

- **selectively bind** to amyloid plaques in mouse and human brain
- do not crossreact with cellular APP or brain cells
- no reactivity with peripheral tissues: **specific**

Histology with antibodies from CAD 106 immunized Rhesus monkeys

APP23 Brain

AD Brain

Staufenbiel, M. et al., 2006
Active immunotherapy: CAD106 first study in AD patients

Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer’s disease: randomised, double-blind, placebo-controlled, first-in-human study

Bengt Winblad, Niels Andreasen, Lennart Minthon, Annette Floesser, Georges Imbert, Thomas Dumortier, R Paul Maguire, Kaj Blennow, Joens Lundmark, Matthias Staufenbiel, Jean-Marc Orgogozo, Ana Graf

- phase I, 52-ws study in 58 mild to moderate AD pts (2 cohorts), aged 50-80 yrs, randomly allocated to receive either CAD 106 or placebo
- primary objectives: safety and tolerability and to identify Aβ-antibody response (responders: patients with Ab-IgG serum titers>16 units at least once during the study)
- 56/58 reported minor adverse events. No cases of meningoencephalitis
- 67% of treated patients in cohort I and 82% in cohort 2 developed Aβ antibody response.
- Phase II: safety and tolerability confirmed (2014)
Ongoing – active – Phase III
“Adaption trial” – CAD 106

- 2014: Novartis partnered with the Banner Alzheimer Research Institute to conduct a secondary prevention trial within the Alzheimer Prevention Initiative.
- This Phase 2/3 trial began in November 2015 and is set to run until 2023, with a 5-year treatment period.
- Aims to enroll 1,340 homozygous ApoE4 carriers between the ages of 60 and 75 who are cognitively normal. About half of participants will be randomized to compare CAD106 to matching placebo injected intramuscularly at weeks 1, 7, 13, 24 and then quarterly

- **Primary outcome**: ability to delay diagnosis to MCI or AD dementia and change on the APICCC cognitive composite (Langbaum et al., 2015).
- **Secondary outcomes**: change on the Clinical Dementia Rating Scale sum of boxes (CDR-SB) along with other cognitive/functional scales, fluid biomarkers including CSF Aβ and tau, brain imaging including volumetric MRI plus amyloid PET and tau PET

ClinicalTrials.gov Identifier: NCT02565511
Verified: Aug 2016
Caveat

Are there concerns on inappropriately labeling individuals with «preclinical Alzheimer’s disease» people who might never progress to manifest dementia in spite of biomarker evidence of amyloid deposition?

In other fields, terms as «precancerous lesions» or «prediabetes» did not raise any ire…..

Apprehension over preclinical AD terminology reflects the stigma of the clinical syndrome of AD

Sperling et al., 2014
Redundant research in AD drug development could be avoided by increased openness. Detailed results, outcomes, and databases of clinical trials should be made broadly available immediately after studies have been completed.

Early-phase clinical trials need to be replicated before drug development moves to later phases.
Thank you for your attention