AND NOW WHAT?
WHERE ARE WEヘADED IN AD DRUG DEVELOPMENT?

Paul Aisen December 6, 2019
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Initial title for this talk:

Failure after Failure: Where do we go from here?

Oct 22, 2019: aducanumab is resurrected

Revised title for this talk:

And now what? Where are we headed in AD drug development?
Tough couple of years: failure after failure

- Verubecestat (February, 2018)
- Atabecestat/EARLY (May, 2018)
- Lanabecestat (June, 2018)
- Crenezumab (January, 2019) continues in API/ADAD
- Aducanumab (March, 2019) now continuing
- Umibecestat/GENERATION (July, 2019)
- Elenbecestat (September, 2019)
Amyloid has been highest on our list of therapeutic targets for decades, but …

- Failure after failure

- After aducanumab, BACEi disappointments, many called for moving on, abandoning existing trials such as A4
Does amyloid deserve the attention it receives?

- So many negative trials
- But still

- By far the strongest rationale
  - Amyloid accumulation begins the disease process
  - Amyloid accumulation is sufficient to predict dementia
  - Amyloid species are highly toxic in many model systems
  - All know genetic causes of AD are tightly linked to amyloid accumulation (APP, PS1, PS2 mutations; Down syndrome)
A major recent disappointment in the field

- BACE inhibitors carry risk of toxicity
  - Rapid onset cognitive worsening seen with multiple BACE inhibitors
  - Increase in hippocampal atrophy (non-progressive)
  - Similar to gamma secretase inhibitors?!
Even more disappointing: Aducanumab Phase 3 stopped early

- Futility analysis results announced March, 2019
- “Independent data monitoring committee advises aducanumab unlikely to meet primary endpoints”
- Very surprising result after highly encouraging Phase 1b
- More scientists and companies give up on amyloid therapeutic hypothesis
But, on October 22, 2019 …

- Aducanumab resurrected
- Additional data collected after futility analysis datalock
- Full analysis hit primary endpoint, plus secondary outcomes, in one Phase 3 trial
- Second trial negative, but supportive data from those with adequate exposure
- Biogen will submit data to FDA for consideration of approval in early 2020
How could this happen?

- Clinical and cognitive data are noisy
- Futility analyses carry risk, loss of statistical power due to “early” decision making
- In this case, dose was increased during trial increasing the risk of misleading interim analysis

- Oct 22 announcement was a big turnaround for the amyloid hypothesis
So where does the amyloid hypothesis stand?

- Previous supportive findings
  - Solanezumab in Expedition: modest (15-20%) slowing of decline in mild dementia across 3 trials
  - Aducanumab Phase 1b: amyloid reduction and slowing of decline
  - BAN2401 Phase 2: amyloid reduction and slowing of decline

- Aducanumab Emerge trial
  - 22% slowing of clinical decline; supportive cognitive and biomarker data; effect would likely have been larger with completed study, highest dose throughout?
  - What about Engage? (supportive data in those with highest exposure)
Anti-amyloid trials

- Need highest tolerable dose
  - ARIA generally manageable
  - Doses of antibodies has been rising (aducanumab, ganterumab, solanezumab)

- Will earlier intervention (eg, in asymptomatic, amyloid positive individuals) yield bigger gains?
  - Seems very likely, though no data yet

- Combination approaches: target both amyloid and tau?
  - Too many uncertainties about anti-tau strategies?
  - Is targeting amyloid sufficient early on?
What about BACE inhibitors?
BACE inhibition: is the cognitive worsening manageable?

- “Symptomatic issue,” mild and non-progressive: verubecestat
  - What about MRI?
- Dose-related: atabecestat
- Reversible: atabecestat
Verubecestat in AD and prodromal AD

Egan et al, NEJM, 2018, 2019
Verubecestat increase in hippocampal atrophy in prodromal AD

Figure S7. Model-based mean (SE) change from baseline in MRI hippocampal volume
EARLY: cognitive effects of atabesestat

These data suggests that adverse cognitive effects may be dose-related and reversible.
We should not give up on BACE inhibition

- The amyloid hypothesis remains *by far* the most compelling basis for disease-modification therapy
- BACE inhibition remains a powerful approach to primary prevention and very early treatment
- Modest, reversible cognitive toxicity can readily be monitored during a trial
- Modest inhibition (25-50%) should be studied in appropriate populations
- We must closely evaluate the coming datasets from elenbecestat and umibecestat trials
- We must continue to pursue basic mechanistic research
- It will not be easy to move forward with BACE inhibitors, but nothing that we do is easy
Costly errors?

- Over-generalizing trial failures
  - Each failure is very specific to trial conditions

- Intolerance to safety challenges
  - Giving up too soon (bapineuzumab?)
  - Keeping doses too low: ARIA
  - Or too high: BACE inhibitors

- Risk of interim analyses (aducanumab is just one example)
Good news for testing amyloid hypothesis

- We can measure brain amyloid longitudinally in humans
- Blood amyloid peptide ratios reflect brain amyloid load
- Brain amyloid can be removed
- Amyloid peptide generation can be inhibited (?)
What’s coming in anti-amyloid studies?

- Aducanumab submission to FDA
- DIAN: gantenerumab, solanezumab in ADAD
- API: crenezumab in ADAD, CAD106 in E4 homozygotes
- BAN2401 (lecanemab) in early AD
- Gantenerumab in early AD
- Donanemab in symptomatic, amyloid and tau PET positive
- A4, A45, A3
- Many other early phase studies
A bit more on the A-platform trials

- A4, as compared to the marginally positive Expedition trials of solanezumab in mild AD dementia
  - Dose increased to 4x that of Expedition
  - Duration 3x that of Expedition
  - A decade earlier stage of AD

- A45: BAN2401 (lecanemab) in preclinical AD

- A3: BAN2401 (lecanemab) in pre-preclinical AD

- Optimism growing
When should we target amyloid?

Ongoing studies in pre-symptomatic Alzheimer’s.

Mostly negative trials (or small effect sizes) in symptomatic AD.

Diagram:
- Cognitive performance, FDG-PET, tau PET, atrophy
- Magnitude of change
- Clinical stage of disease
- Normal, Cognitively normal, MCI, Dementia
- Aβ
- A3 in pre-AD, PP in AD, A4 in pre-clin AD, A45 in pre-clin AD
- Mostly negative trials (or small effect sizes) in symptomatic AD
Other approaches

- Tau
- Microglia
- APOE
- Target misfolded proteins
- Neuroprotection
- Anti-infectives?
- Anti-aging?
- Other: exercise, cognitive, multidomain, target deficiencies (DHA, testosterone)
Challenges with tau

- Absence of genetic support
- Can immunotherapy work against intracellular processes (or can it work to reduce spread)?
- What is the right target/epitope?
Microglia

- TREM2
- Role in plaque clearance

But:

- Complexity of microglial roles is challenging
- Need, specific target, plausible drug candidates
- No good biomarkers to aid development
APOE

△ By far, the most important genetic risk factor for sporadic AD

△ APOE4 increases risk, E2 decreases risk

△ Intriguing case report (Arboleda-Velasquez et al, Nature Medicine, 04 November 2019)
  □ Homozygous APOE3 mutation (Christchurch) protects against dementia despite huge amyloid load in a PS1 mutation carrier
Targeting proteinopathy

- siRNA
- Epigenetic modulation
- Epichaperome
- Immunotherapy?
Essential to continue to test many other hypotheses until we have success

- Particularly in late stage disease, which is very complicated
  - Alpha synuclein
  - TDP-43
  - Vascular disease
  - ...

- Must also test ways to increase brain resilience across the lifespan
Alzheimer’s disease

Cognitive performance, FDG-PET, tau PET, atrophy

Magnitude of change

Clinical stage of disease

NORMA L  COGNITIVELY NORMAL  MCI  DEMENTIA

25+ years
AD and its complications

Increasing proteinopathies

Magnitude of change

Cognitive performance, FDG-PET, tau PET, atrophy

αβ

Clinical stage of disease

25+ years

Normal

Cogitively Normal

MCI

Dementia
AD and its complications

Increasing proteinopathies

Increasing vascular disease

25+ years
AD and its complications

25+ years

Cognitive performance,
FDG-PET, tau PET, atrophy

αβ

Increasing proteinopathies

Increasing vascular disease

Loss of resilience

25+ years

Clinical stage of disease
Prevention and treatment of AD

- Lifelong: promote brain resilience
  - Diet, physical exercise, cognitive exercise, social engagement

- Starting in middle age:
  - Attention to vascular risk (diabetes, hypertension, cholesterol)
  - Monitor plasma abeta ratios for evidence of dysregulation (low dose secretase inhibition as needed)

- If amyloid accumulates in brain:
  - Reduction with amyloid lowering immunotherapy
  - Maintenance with immunotherapy or low dose BACEi
  - Anti-proteinopathy measures (against tau, synuclein, TDP-43)
Lessons from an eventful year

- Be wary of futility analyses and other statistical misadventures
- *The amyloid hypothesis will yield effective therapies*
  - Adverse effects of anti-amyloid therapies, including ARIA and cognitive worsening, may be manageable
- We must continue to pursue other strategies
- We can now take advantage of advances in blood-based biomarkers, even envision primary prevention of AD
- Collaboration and data sharing more important than ever
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