Reversal of cognitive decline: precision medicine approach

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The semantics of “success” in Alzheimer’s trials

Change in Cognitive Performance

- Aducanumab
- Donanemab
- No Treatment

* https://www.alzforum.org/therapeutics/ducanumab
Alzheimer’s: Pandemic Without Vaccine

• FOR PERSPECTIVE: COVID-19 has killed over 500,000 Americans; Alzheimer’s will lead to death in nearly 100 times that many of the currently living Americans.

• THE PROBLEM: Whereas COVID-19 is a simple disease of known etiology and prevention, Alzheimer’s is a complex disease of unknown etiology and >400 failed clinical trials.

• FUNDAMENTAL NATURE of Alzheimer’s is what is needed, a model that is consistent with the >150,000 papers published, and will predict therapeutic success and failure accurately.
Simple illness: e.g., pneumococcal pneumonia
Complex illness: e.g., Alzheimer’s disease

- INS-R
- PATHOGENS
- NF-kappaB
- Hg
- MYCO
- ORG
- HCYS

...
Game of Throwns:
Greatest Biomedical Therapeutic Failure

- Dimebon x2
- Semagacestat
- Rosiglitazone
- AN-1792
- Alzhemed
- Flurizan
- Rember
- Bapineuzumab
Theories of Alzheimer’s

• Amyloid cascade
• Tau
• Prion
• Type 3 diabetes
• Chronic *Herpes simplex* infection
• Gingipain produced by *P. gingivalis*
• Mercury toxicity
• Metal binding by amyloid
• Reactive oxygen/nitrogen species
• APP amplification
• Cortical demyelination
• Vascular leak
CURRENT STANDARD OF CARE

CURRENT STANDARD:

1 Cause (Unknown) 1 Disease 1 Rx MonoRx, 1 Phase, Ineffective

RESEARCH FINDINGS:

36 Contributors 6 Subtypes Many Rx Personalized Programs
The Master Switch of Alzheimer’s

Trophic/Anti-Alzheimer’s  Anti-Trophic/Pro-Alzheimer’s

sAPPα  sAPPβ

CTFα  Aβ  J_{casp}  C_{31}
Chronic illnesses as signaling imbalances

Osteoporosis:

Cytoblastic

Cancer:

Synaptoblastic

Alzheimer’s:

Synaptoclastic

Osteoblastic

Osteoclastic

Cytoclastic
Alzheimer’s: a network insufficiency

\[ p(AD) \propto \int_{t=0}^{t} \frac{\sum(\text{synaptoclastic signaling})}{\sum(\text{synaptoblastic signaling})} \, dt \]
Alzheimer’s: major contributors

\[ p(AD) \propto \int \frac{\sum(\text{synaptoclastic signaling})}{\sum(\text{synaptoblastic signaling})} \approx \int \frac{\sum[\text{inflammatory mediators+toxins}]}{\sum[\text{energetics+trophic support}]} \]
The perfect Alzheimer’s drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.
A roof with 36 holes
The 21st-century physician
Functional Medicine:

• Has led to improved outcomes for many illnesses, such as type 2 diabetes, multiple sclerosis, metabolic syndrome, cardiovascular disease, lupus, rheumatoid arthritis, autism spectrum, PANDAS, cognitive decline, et al.

• In order to make functional medicine the standard of care, it will be important to perform clinical trials to prove efficacy that has already been shown repeatedly in anecdotal studies.

• Therefore, we proposed a proof-of-concept trial in which, instead of pre-determining a monotherapeutic Rx, each patient was evaluated to identify the contributors to cognitive decline, and these were targeted.
Goals of Treatment and Prevention

- **Energetics**: ketosis (1.0-4.0 mM BHB or >7 ACEs), cerebral blood flow, oxygenation.
- **Insulin sensitivity**.
- **Trophic support**: growth factors, hormones, nutrients.
- **Resolution of inflammation** and prevention of further inflammation.
- **Treatment of pathogens**, optimization of microbiomes.
- **Detoxification**.
- **Stimulation**: light or magnetic stimulation, brain training.
- **Improve adaptive immune system**, reduce innate (inflamm).
- **Reduce amyloid-beta**.
- **Regeneration**, synaptogenesis.
ReCODE Mobile App

- **App Feature List**
  - Integration with FitBit, Oura Ring, Apple Watch, Ketone Breathalyzer, and more…
  - Snapshot of daily and weekly progress.
  - Push notifications to keep participant on track and engaged.
  - Access to procured content and guides specific to the protocol.
  - Live forums for sharing and learning from fellow practitioners and participants.
  - Access to reports, history as well as results tracking of all other cognitive assessments.
  - Access to participant care teams.
EDWARD: 71 y/o E4/3
MARCY: 74 y/o with AD

Percentile Score within Demographic

Cognition

Hippocampal Volume

Pre-Treatment
Post-Treatment
66 yo man with “senior moments”

- Family history+ in both parents.
- ApoE3/4, amyloid PET markedly positive, FDG-PET typical for AD, hippocampal volume reduced, neuropsych testing MCI.
- Hs-CRP 9.9.
- Homocysteine 15.1.
- Vitamin D 21.
- Testosterone 264, free T3 2.4, TSH 2.21.
- Responded metabolically, cognitively, and volumetrically to ReCODE. Neurologist said he is now “normal.”
<table>
<thead>
<tr>
<th>66M ApoE4/3</th>
<th>2014</th>
<th>2015 (Rx 10 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>9.9</td>
<td>3</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Struggling</td>
<td>Working full-time</td>
</tr>
<tr>
<td>MRI hippocampal volume</td>
<td>17%ile</td>
<td>75%ile</td>
</tr>
</tbody>
</table>
BEFORE: Gray Matter Volume = 419.5 cc

AFTER: Gray Matter Volume = 531.5 cc

23% increase in gray matter volume with treatment.
Prevention and Reversal of Cognitive Decline

Reversal of cognitive decline: A novel therapeutic program

Dale E. Bredesen

Research Paper

Prevention and Reversal of Cognitive Decline

Reversal of cognitive decline in Alzheimer’s disease

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Research Paper

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Key words: neurodegeneration, cognition, biomarkers, dementia, neurophysiology, imaging, Alzheimer’s disease.

Abstract: Alzheimer’s disease is one of the most significant healthcare problems globally and nationally. Recently, the first description of the reversal of cognitive decline in patients with early Alzheimer’s disease or its precursors, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment), was published [1]. The therapeutic approach used was programmatic and personalized rather than monotherapeutic and invariant, and was dubbed multiphasic approach for neurodegeneration (MND). Patients who had to discontinue work were able to improve their performance. The patients, their spouses, and their co-workers, all reported improvements. Here we report the results from quantitative MRI and neuropsychological testing in ten patients with cognitive decline, nine ApoE4+ (five homozgous and four heterozygous) and one ApoE4-, who were treated with their personalized MND protocol for 5-24 months. The magnitude of the improvement is unprecedented, providing additional objective evidence that this programmatic approach to cognitive decline is highly effective. These results have far-reaching implications for the treatment of Alzheimer’s disease, MCI, and SCI, for personalized programs that may enhance the therapeutic potential of new drugs, including anti-amyloid, anti-tau, anti-inflammatory, and anti-neurodegeneration agents, and for the use of biomarkers for both diagnosis and monitoring disease progression.

INTRODUCTION

Alzheimer’s disease is now the third leading cause of death in the United States [1] and the development of effective treatments is a major healthcare goal. However, while all reported for Alzheimer’s disease, there appear to be many potential contributors to Alzheimer’s disease, such as in chronic illnesses such as cardiovascular disease, there may be many potential contributors to Alzheimer’s disease, such as in chronic illnesses such as cardiovascular disease, diabetes, inflammatory diseases, and even neurodegenerative diseases such as Lewy body disease, tauopathies, frontotemporal lobar degeneration, multiple sclerosis, and neuroinfectious diseases.[2] The recent recognition of the role of inflammation and immune activation in Alzheimer’s disease has led to a new paradigm in the treatment of Alzheimer’s disease, with a focus on reducing inflammation and immune activation.

Programmatic and personalized approaches to Alzheimer’s disease may be particularly effective because they address the underlying causes of the disease, rather than just treating symptoms. This may involve reducing inflammation, restoring gut health, and addressing other factors that may contribute to the disease. The personalized approach may also be more effective because it takes into account the individual patient’s unique genetic and environmental factors.

Data from the Precision Medicine and Reversal of Cognitive Decline study, a randomized controlled trial in which 127 patients were randomized to either a personalized treatment plan or a standard treatment plan, showed that the personalized treatment plan was more effective in reversing cognitive decline. The personalized treatment plan involved a combination of lifestyle changes, medication, and supportive therapies, and was tailored to the individual patient’s unique needs.

Conclusion

In conclusion, personalized and programmatic approaches to Alzheimer’s disease may be particularly effective because they address the underlying causes of the disease, rather than just treating symptoms. The use of biomarkers to monitor disease progression and response to treatment may also be particularly important in personalized approaches. Further research is needed to determine the optimal combination of treatments for different patient subgroups.
• First trial in which, instead of pre-determining a treatment, contributors are identified and targeted. Clinicaltrials.gov
• Small, proof-of-concept trial with 25 patients with MCI or early dementia: MoCA scores 19 and above.
• Compares personalized, precision medicine protocol for 9 months to historical outcomes from standard of care.
• Evaluations seek to identify root cause contributors to cognitive decline: pathogens, toxins (metals, organics, biotoxins), genetics, nutrients/trophins/ hormones, immune response, etc.
• MoCA (Montreal Cognitive Assessment) scores determined by outside evaluators at t=0, 3, 6, and 9 months.
• CNS Vital Signs, an on-line cognitive assessment that is more sensitive and more extensive than MoCA, was also performed at t=0, 3, 6, and 9 months. Combining MoCA and CNS-VS created a larger dynamic range and reduced a potential ceiling effect.
• AQ-21 is a subjective assessment of cognitive decline filled out by the patient’s partner.
• AQ-20 is an estimate of change administered at the end of the trial, in which the partner estimates the decline or improvement for each patient.
• MRI with volumetrics (t=0, 9 months).
Improvement in Neurocognitive Index

CNSVS NCI Data

- Baseline
- 3 month
- 6 months
- 9 months

NCI Score

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
• MoCA (Montreal Cognitive Assessment) scores improved: $p = 0.001$. 76% of patients improved.
• Neurocognitive index improved: $p < 0.001$. 84% of patients improved.
• Cognitive subtests improved: verbal memory ($p = 0.007$), executive function ($p < 0.001$), psychomotor speed ($p < 0.001$), cognitive flexibility ($p = 0.013$), et al.
• AQ-20 indicated improvement: $p = 0.005$.
• BrainHQ (brain training) scores improved in all patients.
• MRI: gray matter volume improved in comparison to historical controls with AD, as well as cognitive normals.
• Hippocampal volume declined less than AD and normals.
Goal of AD trials: optimize outcome or income?

Change in Cognitive Performance

- No Treatment*
- Aducanumab*
- Donanemab*
- Trial

* https://www.alzforum.org/therapeutics/aducanumab
• Cognitive decline is reversible for most patients with MCI or early dementia.
• For those whose cognition declines, the likely contributors to decline may be obvious (e.g., continued mycotoxin exposure), but should be sought.
• For those with MoCA scores of 0-18, although there are anecdotes documenting improvement, a separate trial will be required to determine whether a similar functional medicine approach would be successful.
• The feasibility of utilizing the approach in this trial may be improved with simplification, reimbursement/cost reduction, and enhanced training.
• The current study provides strong support for a larger, randomized, controlled trial, and such a trial is planned to include 100 patients.
• A similar approach, modified for the specific mechanisms unique to each neurodegenerative disease, may prove effective where other treatments have failed.
• Combining the results of this trial with the previous finding that there is a decades-long presymptomatic and early symptomatic period suggests that Alzheimer’s disease should now be optional instead of unavoidable.
Just as for leprosy and polio, Alzheimer’s shall become a former scourge.