CTAD Task Force Paper

The Journal of Prevention of Alzheimer's Disease - JPAD
Volume 6, Number

Combination Therapy for Alzheimer's Disease: Perspectives of the EU/US CTAD Task Force

*S. Gauthier[1], J. Alam[2], H. Fillit[3], T. Iwatsubo[4], H. Liu-Seifert[5], M. Sabbagh[6], S. Salloway[7], C. Sampaio[8], J.R. Sims[5], B. Sperling[9], R. Sperling[10], K.A. Welsh-Bohmer[11], J. Touchon[12], B. Vellas[13], P. Aisen[14] and the EU/US/CTAD Task Force**

* EU/US/CTAD TASK FORCE: Bjorn Aaris Gronning (Valby); Paul Aisen (San Diego); John Alam (Cambridge); Sandrine Andrieu (Toulouse), Randall Bateman (St. Louis); Monika Baudler (Basel); Joanne Bell (Wilmington); Kaj Blennow (Mölndal); Claudine Brisard (Blue Bell); Samantha Budd-Haeberlein (USA); Szofia Bullain (Basel) ; Marc Cantillon (Princeton) ; Maria Carrillo (Chicago); Gemma Clark (Princeton); Jeffrey Cummings (Las Vegas); Daniel Di Giusto (Basel); Rachelle Doody (Basel); Sanjay Dubé (Aliso Viejo); Michael Egan (North Wales); Howard Fillit (New York); Adam Fleisher (Philadelphia); Mark Forman (North Wales); Cecilia Gabriel-Gracia (Suresnes); Serge Gauthier (Verdun); Jeffrey Harris (South San Francisco); Suzanne Hendrix (Salt Lake City); Dave Henley (Titusville); David Hewitt (Blue Bell); Mads Hvenekilde (Basel); Takeshi Iwatsubo (Tokyo); Keith Johnson (Boston); Michael Keeley (South San Francisco); Gene Kinney (South San Francisco); Ricky Kurzman (Woodcliffe Lake); Valérie Legrand (Nanterre); Stefan Lind (Valby); Hong Liu-Seifert (Indianapolis); Simon Lovestone (Oxford); Johan Luthman (Woodcliffe); Annette Merdes (Munich); David Michelson (Cambridge); Mark Mintun (Philadelphia); José Luis Molinuevo (Barcelona); Susanne Ostrowitzki (South San Francisco); Anton Porsteinsson (Rochester); Martin Rabe (Woodcliffe Lake); Rema Raman (San Diego); Elena Ratti (Cambridge); Larisa Reyderman (Woodcliffe Lake); Gary Romano (Titusville); Ivana Rubino (Cambridge); Marwan Noel Sabbagh (Las Vegas); Stephen Salloway (Providence); Cristina Sampaio (Princeton); Rachel Schindler (USA); Peter Schüler (Langen); Dennis Selkoe (Boston); Eric Siemers (New York); John Sims (Indianapolis); Heather Snyder (Chicago); Georgina Spence (Galashiels); Bjorn Sperling (Valby); Reisa Sperling (Boston); Andrew Stephens (Berlin); Joyce Suhy (Newark); Gilles Tamagnan (New Haven); Edmond Teng (South San Francisco); Gary Tong (Valby); Jan Torleif Pedersen (Valby); Jacques Touchon (Montpellier); Bruno Vellas (Toulouse); Vissia Viglietta (Cambridge) ; Christian Von Hehn (Cambridge); Philipp Von Rosenstiel (Cambridge) ; Michael Weiner (San Francisco); Kathleen Welsh-Bohmer (Durham); Iris Wiesel (Basel); Haichen Yang (North Wales); Wagner Zago (South San Francisco); Beyhan Zaim (Woodcliffe Lake); Henrik Zetterberg (Mölndal)

1. McGill Center for Studies in Aging, Verdun QC, Canada; 2. EIP Pharma Inc., Cambridge MA, USA; 3. The Alzheimer's Drug Discovery Foundation, New York NY, USA; 4. University of Tokyo, Japan; 5. Eli Lilly and Company, Indianapolis IN, USA; 6L Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas NV, USA; 7. The Warren Alpert Medical School of Brown University, Providence RI, USA; 8. CHDI Foundation, Princeton NJ, USA; 9. Lundbeck, Valby 2500 Denmark; 10. Brigham and Women's Hospital, Boston MA, USA; 11. Duke University, Durham NC, USA; 12. University Hospital of Montpellier, 34025 Montpellier Cedex 5, and INSERM 1061, France; 13. Gerontopole, INSERM U1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France; 14. Alzheimer's Therapeutic Research Institute (ATRI), Keck School of Medicine, University of Southern California, San Diego CA, USA

Corresponding Author: Serge Gauthier, McGill Center for Studies in Aging, Verdun QC, Canada, serge.gauthier@mcgill.ca

J Prev Alz Dis
Published online April 18, 2019, http://dx.doi.org/10.14283/jpad.2019.12

Abstract

Combination therapy is expected to play an important role for the treatment of Alzheimer's disease (AD). In October 2018, the European Union-North American Clinical Trials in Alzheimer's Disease Task Force (EU/US CTAD Task Force) met to discuss scientific, regulatory, and logistical challenges to the development of combination therapy for AD and current efforts to address these challenges. Task Force members unanimously agreed that successful treatment of AD will likely require combination therapy approaches that target multiple mechanisms and pathways. They further agreed on the need for global collaboration and sharing of data and resources to accelerate development of such approaches.

Key words: Alzheimer's disease, amyloid, tau, therapeutics, trial design.

Introduction

Combination therapy has resulted in improved outcomes for many of the world's most significant and complex diseases, including cancer, AIDS, and cardiovascular disease, and the prospect of combination therapy has also gained traction in the Alzheimer's disease (AD) field (1-3). The reasons for pursuing combination therapy for AD go beyond the disappointing track record in developing effective treatments for this disease that is likely to affect more than 150 million people worldwide by 2050 (4-6). As with many other complex diseases, AD arises from a series of pathological changes and the involvement of many pathogenic pathways that begin well before symptoms appear (7), suggesting that effective treatment will require targeting multiple pathways, either simultaneously or sequentially. However, the complexity of AD pathophysiology also introduces substantial hurdles to the development of combinatorial approaches. To better understand current efforts to develop such approaches and the steps that need to be taken to expedite this process, the European Union-North American Clinical Trials in Alzheimer's Disease Task Force (EU/US CTAD Task Force) discussed combination therapy for AD at its 2018 meeting. The Task Force brings together investigators from industry, academia, and regulatory agencies to build consensus and promote collaboration and information sharing on issues important for the development of effective Alzheimer's treatments. Many Task Force members expect combination therapy to play an important role in treating AD and call for global collaboration to develop combination therapies (8, 9), but agree that the path forward has yet to be clearly defined.

Received March 8, 2019
Accepted for publication March 15, 2019

Best candidates for combination therapy

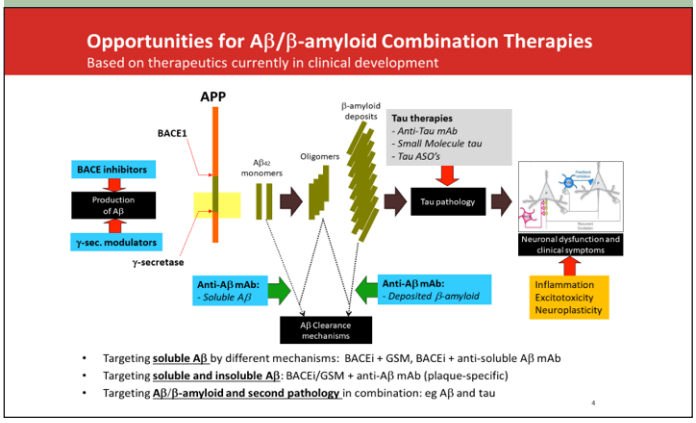
Combination therapy for AD could involve interrupting a single important pathogenic pathway (such as amyloid or tau) at multiple points or targeting two or more pathways together (such as amyloid plus tau). Despite the many disappointing clinical trials of disease-modifying therapies targeting amyloid, it remains a promising target for disease modification, in particular for prevention studies. The rationale for targeting amyloid is strong (10). Most known genetic mutations related to AD are involved in amyloid production or processing. This includes mutations in the Presenilin 1 and 2 and amyloid precursor protein (APP) genes, and Down syndrome, the most common cause of early-onset AD, which is caused by a trisomy of chromosome 21 where the APP gene resides. In addition, a mutation in the APP gene known as the Icelandic mutation (A673T) has been shown to be protective against AD and cognitive decline (11).

Moreover, there is abundant evidence that Aβ oligomers and amyloid plaques are toxic (12, 13), and encouraging although preliminary evidence that removing plaques may be associated with improved cognition and clinical outcomes.

The APP molecule undergoes sequential cleavage via β- and γ-secretases to produce amyloidogenic fragments. Amyloid peptides take on monomeric, oligomeric, and fibrillar forms that may cause toxicity through a variety of mechanisms including oxidative stress, excitotoxicity, synaptic failure, and other mechanisms associated with neuronal death (14). This complex pathway from APP to toxicity thus creates multiple potential therapeutic targets (Figure 1). Antibodies directed at different amyloid fragments have been developed as potential treatments against AD with varying degrees of success at removing amyloid and halting the disease process; secretase inhibitors have also been effective at reducing amyloid load but have been associated with cognitive worsening and other adverse events (15, 16).

A workgroup of the National Institutes on Aging and the Alzheimer's Association (NIA-AA) recently published a research framework that defines and stages the disease according to the presence of Amyloid (A), Tau (T) and neurodegeneration (N) biomarkers (17). Yet while the AD disease-modifying drug development pipeline continues to reflect the predominance of the amyloid pathway, there has recently been an increase in the number of drug trials testing non-amyloid mechanisms (18, 19). In agreement with the NIA-AA Research Framework, the Task Force recognized the need to add biomarkers of other pathologies commonly seen in the brains of people with AD, such as vascular pathology (V), inflammation (I), and Lewy bodies (L).

Figure 1. Opportunities for amyloid-based combination therapies based on therapeutics currently in clinical development



Possible combination trial designs that target amyloid

Preclinical AD is marked primarily by amyloid accumulation, with cognitive performance and biomarkers of neurodegeneration, tau, and cerebral metabolism increasing markedly only in the clinical stages of disease (20). This suggests that a vigorous attack on amyloid using multiple agents simultaneously to target different steps in the amyloid pathway may slow, stop, or reverse the progression of AD.

However, an even more promising approach may be attacking the amyloid pathway sequentially at different times and disease stages. Sequential therapy offers efficiency advantages by enabling the assessment of individual adverse events and benefits more readily. One potential sequential therapy design using an induction/maintenance approach would be to start treating with an inhibitor of Aβ production, such as a beta-secretase inhibitor (BACEi), before there is any detectable amyloid; and then introducing amyloid-reducing antibodies when amyloid becomes elevated but before neuronal damage has begun. This approach could reduce the number of anti-amyloid antibody infusions required, thus saving costs and reducing exposure. However, designing a trial using this strategy could become very complicated.

An alternative would be to start with an anti-amyloid antibody first to induce an amyloid-free state for 3 months to 1 year (long enough to see cognitive benefit in early stage), and then push backwards and treat with BACEi as maintenance therapy. Although BACEi have shown significant adverse events in several trials, a lower dose (e.g. inhibiting only ≤30% of BACE) may improve the risk/benefit calculation. Other secretase modulators, antibodies that target diffusible amyloid, or amyloid active vaccine may also be used for maintenance.

A combination study including both anti-tau and anti-amyloid drugs also has been suggested although many questions remain about the efficacy of anti-tau agents, the

best tau epitopes to target, the optimal stage of disease to treat, how to establish target engagement, and how to design anti-tau trials (31). Another combination clinical trial that combines two non-amyloid approaches is also underway at Amylyx Pharmaceuticals in partnership with the Alzheimer's Drug Discovery Foundation and the Alzheimer's Association. This Phase 2 trial of AMX0035 combines sodium phenylbutyrate, which is approved for the treatment of urea cycle disorders, and tauroursodeoxycholic acid (TUDCA), a bile acid that supports mitochondrial energetics (19). The combination is expected to protect neurons from inflammation and oxidative stress.

Best target populations and study designs

For clinical trials of combination therapies such as those described above, the stage of disease and study design for proof-of-concept and Phase 3 studies will be determined by a medication's mode of action on disease pathophysiology. For example, trials designed to treat patients in early disease stages, i.e., symptomatic with a CDR 0.5 or 1, should maximize the likelihood of detecting disease progression during the trial and demonstrating a slowing of progression if the treatment is efficacious. Enabling optimal designs and optimizing treatment assignment will require that participants have adequate biological characterization with biomarkers.

The most informative trial design for a two-agent combination therapy trial would employ a 2 x 2 factorial structure where each agent is tested alone and in combination (21). A more efficient approach, however, would be a 2-arm trial of the combination vs. placebo, with deconvolution of the contribution of each agent should the initial approach be successful. In either case, selecting dose and treatment regimens for combination studies is complicated and often leads investigators to take shortcuts, which can lead to misleading results or unacceptable risks to participants. The statistical and regulatory implications of various trial designs are discussed below.

For trials in patients with AD dementia, since many individuals will already be taking acetylcholinesterase inhibitors (e.g., donepezil) and/or memantine (22), add-on designs that combine the standard treatment plus the disease-modifying agent being tested may be necessary. To test combinations in early AD patients, a different type of add-on design could provide more precision. For this type of study, participants would be randomized first to induction therapy with an agent that targets the most prominent apparent pathology (amyloid for most, tau for a few); then after a pre-determined time period (e.g., 6 months), a second treatment is added that targets the second most predominant pathology (e.g., tau, amyloid, inflammation, Lewy bodies, or vascular).

Open perpetual platform trials using a master protocol with defined inclusion and exclusion criteria may be the most efficient way to conduct combination trials. The Dominantly Inherited Alzheimer's Network Trials Unit (DIAN-TU) has developed such a platform for testing a variety of therapeutics in people with autosomal dominant AD (23). Such platforms enable testing of multiple active treatment arms with shared control arm, and they allow for: 1) pooling of placebo groups, 2) the discontinuation of arms for futility, 3) the addition of new arms including either new drugs or new doses, 4) adaptive randomization, and 5) personalization of arms to specific subgroups (24).

Regulatory issues

Regulatory authorities encourage innovative development approaches for delivering combination therapies for AD. In 2013, the U.S. Food and Drug Administration (FDA) published guidance for co-development of two or more new investigational drugs for use in combination (25). According to this guidance, combination therapy is justified for treating serious diseases with unmet medical needs when there is a strong rationale and strong preclinical data for the combination, and when there is a compelling reason for developing the two drugs in tandem rather than independently.

Selecting agents to combine begins with assessing and characterizing whether the interaction between the components is additive, synergistic, or antagonistic. In addition, since most amyloid treatments activate the immune system, nonclinical studies are needed to assess the interaction of combinations with immune mechanisms. How the effectiveness of the combination is defined affects the study design and may depend on the stages of development of the components. Thus, if one component is already approved, it may be sufficient to demonstrate how much greater is the effect of the combination of new drug plus the approved drug compared to the effect of the approved drug alone. If both components are novel, however, a full factorial design may be needed to understand contributions of the different agents to the treatment response. Additive or synergistic effects may be demonstrated.

Both FDA and the European Medicines Agency (EMA) require preclinical studies of the combination. In some cases, toxicology of the combination will need to be tested, although there have been some studies where regulators were sufficiently confident that a combination would be safe and allowed advancing to Phase 2.

Blazing the trail to combination therapy

In December 2017, Lilly launched the multi-site TRAILBLAZER-ALZ Phase 2 trial, which combined a BACEi with the anti-amyloid monoclonal antibody LY3002813 (NCT03367403), a humanized IgG1 antibody directed at N3pG, an amyloid epitope that is present only

in amyloid plaques (26). In preclinical studies, LY3002813 was shown to remove amyloid plaque through microglial-mediated clearance (27). In the PDAPP mouse model, an antiN3pG plus a BACEi removed most pre-existing plaque and improved neuronal health in a synergistic, dose-dependent manner (28).

A phase 1 study of the monoclonal antibody demonstrated a significant reduction in brain amyloid by florbetapir positron emission tomography (PET); and a phase 1 study of the BACEi demonstrated a lowering of cerebrospinal fluid (CSF) Aβ, with no safety or tolerability concerns. These results in Phase 1, combined with the preclinical data, prompted Lilly to plan the TRAILBLAZER trial that would include three arms: 1) placebo, 2) N3pG monoclonal antibody alone, and 3) N3pG mAb plus BACEi. Rather than using a full factorial design, external data from multiple ongoing BACEi studies would be used to demonstrate the efficacy of the BACEi alone.

The study enrolled participants with early symptomatic AD who are amyloid positive with a low-to-medium tau burden, randomized to the three arms. These inclusion/exclusion criteria were selected to produce a relatively homogeneous population. A composite scale of cognition and function was selected as the primary outcome, and a robust biomarker strategy was planned to demonstrate the contribution of each component of the combination (29). Other cognitive and functional measures as well as amyloid PET, tau PET, and volumetric magnetic resonance imaging (MRI) were included as secondary outcome measures.

The combination BACEi plus N3pG mAb arm of the trial was subsequently discontinued based on data from multiple sources that raised concerns about the risk/benefit profile of BACEi (30). Nonetheless, the study design holds lessons for future trials of combination therapies, including the use of preclinical data in animal models to demonstrate synergy, the use of robust Phase 1 data to simplify Phase 2 combination designs, and the importance of early interaction with regulators to design toxicology and clinical studies.

Moving forward

Despite the discontinuation of the combination therapy arm in the TRAILBLAZER trial, Task Force members unanimously agreed that successful treatment of AD will require combination approaches that target multiple mechanisms and pathways. However, many questions remain regarding how best to move forward in the development of combination therapies.

Task Force members suggested several steps that should be taken to expedite the development of combination therapies:

- Establish thresholds for pathologies beyond amyloid and tau, including inflammation and vascular load.
- Pool observational studies to determine natural history of various combinations of pathologies.
- Negotiate a DIAN-like structure with global resources from companies and academia, for example through the European Prevention of Alzheimer's Dementia Consortium (EPAD).
- Enlarge the dialogue about combination therapy to include disease modifying as well as symptomatic treatments and mechanisms that address the neurodegenerative process.
- Pool resources, for instance by testing add-on compounds in participants enrolled in preclinical or Phase 2 clinical trials with a single agent, having completed the double-blind placebo-controlled phase of the study.

Task Force members also agreed that patient engagement is key to the development of combination therapies, particularly for treatments intended for the presymptomatic stages of the disease.

Acknowledgements: The authors thank Lisa J. Bain for assistance in the preparation of this manuscript.

Conflicts of interest: The Task Force was partially funded by registration fees from industrial participants. These corporations placed no restrictions on this work. Dr. Gauthier reports personal fees from TauRx, Lundbeck Institute, and Esai; and grants from Lilly and Roche, outside the submitted work. Dr. Alam reports personal fees (employment) from EIP Pharma, Inc, outside the submitted work. Dr. Fillit discloses the following consulting relationships during the past 3 years: Axovant, vTv, Lundbeck, Otsuka, Lilly, RTI, Roche, Genentech, Merck, Samus, Pfizer. He reports no conflicts of interest related to these disclosures that are relevant to this publication. Dr. Iwatsubo has nothing to disclose. Dr. Liu-Seifert reports other from Lilly, outside the submitted work. Dr. Sabbagh has consulted for Allergan, Biogen, Bracket, Neurotrope, Cortexyme, Roche, Grifols, Sanofi, VTV therapeutic, and Alzheon. Dr Ssllоway has nothing to disclose; Dr. Sims, employee of Eli Lilly and Company and holder of stock in Eli Lilly and Company. Dr. Sperling is an employee of H. Lundbeck A/S, outside the submitted work. Dr. Sperling reports grants from Janssen, during the conduct of the study; personal fees from AC Immune, personal fees from Biogen, personal fees from Roche, personal fees from Eisai, personal fees from Insightec, personal fees from Takeda, personal fees from Merck, personal fees from General Electric, outside the submitted work. Dr. Welsh-Bohmer has contracts with Takeda Pharmaceutical Company and with VeraSci where she is the VP for Neurodegenerative Disorders. Dr. Touchon has nothing to disclose; Dr. Vellas reports grants from Lilly, Merck, Roche, Lundbeck, Biogen, grants from Alzheimer's Association, European Commission, personal fees from Lilly, Merck, Roche, Biogen, outside the submitted work; Dr. Aisen reports grants from Lilly, personal fees from Proclara, other from Lilly, other from Janssen, other from Eisai, grants from Janssen, grants from NIA, grants from FNIH, grants from Alzheimer's Association, personal fees from Merck, personal fees from Roche, personal fees from Lundbeck, personal fees from Biogen, personal fees from ImmunoBrain Checkpoint, outside the submitted work.

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