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Mini Review

Untangling Developments in Research on the Pathophysiology and Treatment of Alzheimer's Dementia

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Abstract

This commentary evaluates the ongoing interest in the amyloid hypothesis in light of the claimed positive phase 2 trial results for BAN2401. We provide a discussion of the validity and value of the amyloid hypothesis in light of new research developments, with the view and intent toward broadening the lens through which we develop more precise investigation methods to potential treatment options for Alzheimer's dementia.

Keywords: *Alzheimer's Dementia; Amyloid Hypothesis; Amyloid-β; Neuropolicy*

Introduction

The recent reports of positive outcomes in the phase 2 trial of BAN2401 have been regarded as somewhat controversial [1-3]. The results of this amyloid protofibril clearing agent may shed new - and we believe important and necessary - light on the amyloid hypothesis of Alzheimer's dementia (AD), which posits that that the accumulation of amyloid-β peptide initiates the neurodegenerative process.

The reported success of the BAN2401 trial is in contrast to outcomes of prior trials of solanezumab, verubecestat and lanabecestat. Solanezumab, an antibody developed to target amyloid-β, failed to slow cognitive decline via decreasing amyloid-ß accumulation in the brain. Verubecestat and lanabecestat are beta-secretase 1 cleaving enzymes that are theorized to slow the progression of AD by preventing the buildup of amyloid-ß; both drugs failed to show functional amelioration of symptoms in mild-late stage AD patients, which led to the termination of further studies of these agents [4]. BAN2401, a monoclonal antibody that selectively binds soluble amyloid-ß protofibrils, is claimed to significantly mitigate cognitive impairment in AD patients.

Such differing outcomes of the efficacy of amyloid protofibril clearing agents may prompt questions about an understanding of the relationship of amyloid-ß and AD [3,4]. It remains unclear whether plaque accumulation leads to, causes or is in some other way involved in the pattern and extent of cognitive decline seen in AD. Plaques have been found in brains of many elderly people with normal cognition. Plaque formation and physiology can be varied and may initially play a protective role against AD [5,6]. Signs and symptoms of cognitive decline of AD have also been correlated to the number and location of tau tangles [7,8]. The complexity of the relationship of tau tangles and amyloid-ß plaques in the initiation and advancement of cognitive decline brings into stark relief both the dynamic pathophysiology of AD, and the potential viability and value of a multifaceted (rather than singularly focal) therapeutic approach.

Although Biogen and Eisai have claimed that BAN2401 shows promise [1-3], the independent data monitoring c (IDMC) asserted that the drug "did not meet the criteria for success" in late December. Biogen and Eisai countered these assertions, instead citing the improper use of statistical techniques [3]. Clearly additional studies are required, both to more fully disambiguate outcomes and effects, and to provide additional and deeper insight to the role(s) of amyloid- ß in the initiation and progression of AD, and in so doing, provide basis for more precise diagnostics and treatment(s).

Future Opportunities

Recent evidence suggesting that tau protein could be an essential factor in the initiation of AD. Roles of amyloid precursor protein (APP), a transmembrane protein associated with neuronal development, neurite outgrowth, and axonal transport, has been studied in conjuncture with tau. Based upon recent studies, it has been theorized that AD is initiated by impairment of APP metabolism, which then progresses through tau protein, and not necessarily - or exclusively - amyloid-ß pathology [6,7]. These studies reflect, and are reliant upon the development and use of increasingly more sophisticated and precise neurodiagnostic tools and methods.

Studies such as Imaging Dementia Evidence for Amyloid Scanning in the United States, and European Union's Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) project are aimed at further advancing the use of state-of-the-art neurotechnologies, and contribute to and sustain the momentum of large-scale neuroscientific initiatives (e.g. the US' Brain Research through Advancing Innovative Neurotechnology - BRAIN initiative; EU Human Brain Project, as well as newer efforts including the Japan Brain-MIND Project, China Brain Project, among others). Coupled with and synergized by international enterprises (e.g. International Neuroinformatics Coordinating Facility, INCF) in creating coordinated systems of data gathering, assimilation, and synthesis, these programs could enable more granular, and accurate elucidation of the pathologic variables of AD, which in turn could promote the development of more effective approaches to prevention and therapeutics [8-10].

Conclusion

In looking to the future of research, diagnosis, and treatment of AD, it will be important to take measure and learn from the past. Current knowledge of the pathophysiology of AD is expanding, and the development of new diagnostics and therapeutics, such as BAN2401 have merit. Amyloid-based drug targets certainly have potential to become valid treatment options; but, valuable alternative hypotheses of AD pathophysiology exist and should also be thoroughly investigated. Toward such goals, resources must be allocated to studies that both broaden the scope of our understanding of AD, and which better define specific mechanisms and variables that may foster improved assessment and care. As well, regulations, procedures and policies for advancing experimental drugs and devices through phases of development, evaluation of safety and efficacy, and approval should sustain ongoing investments in research, and make emerging products viable for sound clinical use. In this regard, the new programs of US Food and Drug Administration (FDA) are of note and value [11] and should work in concert to encourage and engage similar initiatives of other nations, worldwide. For while we seek to further understand and mitigate the deleterious effects of plaques and tangles of AD, it is - and will be ever more - essential that (research, funding and policy) endeavors to do so be as tangle free as possible.

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