Controversies in Neurology 2016

Is beta-amyloid still a relevant target in AD therapy? Yes!

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The development of disease modifying therapies for Alzheimer disease (AD) is an extremely important goal that has become the focus of major public health initiatives involving governments, civil society, academia and the pharmaceutical industry. The "amyloid cascade" hypothesis of AD is one of the best understood elements of the pathophysiology of this disease, and is based on strong pathological, preclinical and genetic data, including familial and early onset AD and the role of risk factors associated with the production and clearance of amyloid protein, such as ApoE4 genotypes and variants in the APP associated with BACE cleavage.

Based on this hypothesis, amyloid-targeting therapies have been the focus of drug development for the past 2 decades. Several different approaches to remove amyloid, employing both active and passive immunization therapies, as well as enzymatic inhibition of the production of amyloid-beta peptides have been tested in large scale clinical trials. So far all these trials failed to produce clinically meaningful results, or have highlighted significant safety risks for gamma secretase and BACE inhibitors.

This has led many in the field to question the validity of the amyloid hypothesis and to calls to abandon pharmaceutical research on this target. However, the other side of the story of amyloid-targeting therapies has been one of continuous improvement and learning about AD. Data from several of the recently reported trials with anti-amyloid antibodies have shown consistent trends for efficacy in earlier stages of AD, especially in patients receiving higher doses of antibody. At the same time, key advances in diagnostic criteria, including the use of high quality molecular testing of CSF for amyloid and tau proteins, and the widespread use of PET imaging for amyloid (and development of ligands for Tau), have made it operationally feasible to identify the right patients for trials, and to use pharmacodynamic measures to predict therapeutic doses. Finally, our understanding of trial methodology, including the selection and behavior of clinical endpoints in these populations, and identifying predictors of progression, has improved significantly. While there are still doubts about which of the amyloid species in the cascade is the optimal target for therapy, there is founded hope that current trials being conducted with high-dose anti-amyloid antibodies and BACE inhibitors in prodromal and mild AD will be successful.

Nonetheless, the pathophysiology of AD is very complex and involves several other mechanisms and targets beyond amyloid (e.g. p-Tau, inflammation, ER stress, authophagy), and the future of AD treatment will likely be in combination therapies that include targeting amyloid and some if not all of these additional mechanisms to maximize efficacy. Therefore, even if anti-amyloid therapies may not provide a cure for AD, they are very likely to be the first medicines to show disease modifying properties and will remain one of the cornerstones of therapy in the future.