Limits in the design and interpretation of controlled clinical trials based on anti-amyloid agents

A. Padovani

Dip. Scienze Cliniche e Sperimentali, Università degli Studi Health and Wealth di Brescia

The symptomatic drugs currently for Alzheimer's disease (AD) have no effect on disease progression. The type of drug that has developed most rapidly in the last decade is immunotherapy: vaccines and, especially, passive vaccination with monoclonal antibodies. Antibodies are potentially effective drugs as they can be made highly specific for their target and often with few side effects. Data from recent clinical AD trials indicate that a treatment effect by immunotherapy is possible, providing hope for a new generation of drugs. The first anti-amyloid-beta (anti-Aβ) vaccine was halted in phase 2 because of aseptic meningoencephalitis. However, in a follow-up study, patients with antibody response to the vaccine demonstrated reduced cognitive decline, supporting the hypothesis that Aβ immunotherapy may have clinically relevant effects. Bapineuzumab, a monoclonal antibody targeting fibrillar Aβ, was stopped because the desired clinical effect was not seen. Solanezumab was developed to target soluble, monomeric Aβ. In two phase 3 studies, Solanezumab did not meet primary endpoints although when data from the two studies were pooled, a positive pattern emerged, revealing a significant slowing of cognitive decline in the subgroup of mild AD. Different hypotheses have been put forward to explain the failure of such approach so far including either lack of target engagement or amyloid not being the main target. However, before rejecting the amyloid hypothesis, experiences from the field indicate the importance of initiating treatment early in the course of the disease and of enriching the trial population by improving the diagnostic accuracy. Other encouraging efforts in immunotherapy as well as in the small-molecule field offer hope for new innovative therapies for AD in the future.