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Biotherapies in neurological diseases

Amyloid beta peptide immunotherapy in Alzheimer disease

Immunothérapie anti-amyloïde dans la maladie d'Alzheimer

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ABSTRACT

Recent advances in the understanding of Alzheimer's disease pathogenesis have led to the development of numerous compounds that might modify the disease process. Amyloid β peptide represents an important molecular target for intervention in Alzheimer's disease. The main purpose of this work is to review immunotherapy studies in relation to the Alzheimer's disease. Several types of amyloid β peptide immunotherapy for Alzheimer's disease are under investigation, active immunization and passive administration with monoclonal antibodies directed against amyloid β peptide. Although immunotherapy approaches resulted in clearance of amyloid plaques in patients with Alzheimer's disease, this clearance did not show significant cognitive effect for the moment. Currently, several amyloid β peptide immunotherapy approaches are under investigation but also against tau pathology. Results from amyloid-based immunotherapy studies in clinical trials indicate that intervention appears to be more effective in early stages of amyloid accumulation in particular solanezumab with a potential impact at mild Alzheimer's disease, highlighting the importance of diagnosing Alzheimer's disease as early as possible and undertaking clinical trials at this stage. In both phase III solanezumab and bapineuzumab trials, PET imaging revealed that about a quarter of patients lacked fibrillar amyloid pathology at baseline, suggesting that they did not have Alzheimer's disease in the first place. So a new third phase 3 clinical trial for solanezumab, called Expedition 3, in patients with mild Alzheimer's disease and evidence of amyloid burden has been started. Thus, currently, amyloid intervention is realized at early stage of the Alzheimer's disease in clinical trials, at prodromal Alzheimer's disease, or at asymptomatic subjects or at risk to develop Alzheimer's disease and or at asymptomatic subjects with autosomal dominant mutation.

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RÉSUMÉ

Les progrès récents dans la compréhension de la maladie d'Alzheimer ont mené à l'élaboration de nombreuses molécules qui pourraient modifier l'histoire naturelle de la maladie. La voie amyloïde représente une cible importante pour les essais thérapeutiques en cours. L'objectif principal de ce travail est d'examiner les études d'immunothérapie en rapport avec la maladie d'Alzheimer. Plusieurs types d'immunothérapie anti-amyloïde dans la maladie d'Alzheimer sont à l'étude, une immunisation active et passive avec l'administration d'anticorps monoclonaux ciblés sur la voie amyloïde. Bien que les approches d'immunothérapie ont donné lieu à une clearance des plaques amyloïdes chez les patients atteints de la maladie d'Alzheimer, elles n'ont pas encore montré d'effet cognitif significatif pour le moment. Actuellement, plusieurs approches d'immunothérapie ciblant la voir amyloïde sont à l'étude, mais aussi contre la pathologie tau. Les résultats des études d'immunothérapie dans les essais cliniques indiquent que l'intervention pourrait être plus efficace dans les stades plus précoces de la maladie, en particulier le solanezumab avec un impact potentiel sur la maladie de Alzheimer à un stade léger, ceci soulignant l'importance de diagnostiquer la maladie d'Alzheimer le plus tôt possible. Dans les 2 récents essais de phase III avec le solanezumab et le bapineuzumab, l'imagerie TEP a révélé que près d'un quart des patients n'avaient de phénotype amyloïde au départ de l'étude, ce qui suggère qu'ils n'avaient de maladie d'Alzheimer. Ainsi, une nouvelle phase 3 avec le solanezumab appelé Expédition 3, chez les patients atteints d'une maladie d'Alzheimer à un stade léger et la preuve de la présence de lésions amyloïdes cérébrales a récemment débuté. Ainsi, actuellement, l'intervention est réalisé à un stade précoce de la maladie d'Alzheimer dans les essais cliniques, à un stade prodromal, ou parfois même chez des sujets asymptomatiques ou à risque de développer la maladie d'Alzheimer et/ou chez des sujets asymptomatiques avec mutation autosomique dominante.

1. Introduction

The main purpose of this work is to review immunotherapy studies in relation to the Alzheimer's disease (AD). To review the efficacy and safety of immunotherapy drugs, we used the database MEDLINE. We reviewed the English-language, clinical trials designed to evaluate the efficacy or/and safety of immunotherapy drugs, from January 1999 through January 2014.

The cholinesterase inhibitors and memantine have been approved to enhance cognition in AD patients. However, the effects of these treatments are limited and their clinical relevance debated [1]. Recent advances in the understanding of AD pathogenesis have led to the development of numerous compounds that might modify the disease process.

1.1. *Amyloid pathway in drug discovery for Alzheimer's disease*

AD is characterized by a robust neuropathological signature. The AD brain is characterized by a decrease in the number of neurons in the limbic and association cortices and in certain subcortical nuclei projecting to them. The most obvious neuropathological changes in the AD brain are the amyloid plaques and the neurofibrillary tangles (NFT). These 2 lesions occur in the hippocampus, amygdale association cortices, and certain subcortical nuclei. They are often accompanied by variable numbers of amyloid-containing microvessels (congophilic amyloid angiopathy, CAA).

Currently available evidence strongly supports the position that the initiating event in AD is related to abnormal processing of Aβ [2], ultimately leading to formation of Aβ plaques in the brain. Senile plaques are classified as 2 main types: diffuse and compact plaques. The major component of both types of senile plaques is the amyloid β peptide (Aβ). Aβ represents an important molecular target for intervention in AD, and agents that can prevent its formation and accumulation or stimulate its clearance might ultimately be of therapeutic benefit. Potential inhibitors of the β and γ secretase enzymes (which are required for the production of Aβ) are under investigation, but an alternative strategy involving Aβ immunotherapy is attracting much attention.

1.2. *Different approaches of immunotherapy*

Several types of immunotherapy for AD are under investigation [3]. The first, direct immunization with synthetic intact $A\beta_{42}$ has been evaluated in transgenic mouse models and has recently provided the first clinical experience of Aβ immunotherapy. This approach stimulates T-cell, B-cell and microglial immune responses. A second method of active immunization involves the administration of synthetic fragments of Aβ conjugated to a carrier protein avoiding the potential problems associated with mounting a T-cell response directly against Aβ. The third type of immunotherapy under investigation

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