EDITORIAL

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A β immunotherapy for Alzheimer's disease: where are we?

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First draft submitted: 18 January 2016; Accepted for publication: 25 January 2016; Published online: 27 May 2016

Alzheimer's disease (AD) was implicated in most of the estimated 46.8 million worldwide dementia cases in 2015, with projections set to almost triple by 2050 [1]. Because current therapies are focused on ameliorating AD symptoms instead of targeting the underlying causes of the disease, it is necessary to develop disease-modifying therapies.

In accordance with the amyloid cascade hypothesis, AD is caused by the progressive aggregation of the A β peptide into oligomers, fibrils and amyloid plaques, which results on synaptic loss, neuronal dysfunction and cell death [2]. Accumulation of the A β peptide is thought to start more than a decade before the onset of clinical symptomatology, at what is known as the prodromal phase. Then, the first clinical symptoms appear as mild cognitive impairment (MCI) and the disease finally results in dementia. Actually, amyloid deposition can be visualized by PET in the prodromal phase, as well as biochemical changes measured in the cerebrospinal fluid.

A β immunotherapy is a promising approach to reduce A β burden, as illustrated by the large number of ongoing clinical trials [3]. Active A β -immunotherapy uses synthetic full-length A β peptide, or a fragment, to stimulate B cells to generate specific antibodies for sequestering amyloid from the brain in the peripheral system. The first Phase IIa clinical trial for an active AD vaccine, AN1792, contained the full-length A β_{42} peptide and was performed in 2002 (ELAN, Dublin, Ireland, and Wyeth, PA, USA) [4]. Although some beneficial effects were shown by antibody responders, administrations were halted due to the development of meningoencephalitis in approximately 6% of the treated group. Similarly, T-cell meningoencephalitis was noted in two post-mortem reports. It is likely that one of the excipients of the administered preparation induced the exposition to the solvent of the C-terminus of the peptide, which is thought to activate the T-helper type 2

KEYWORDS

- Alzheimer's disease • amyloid- β
- immunotherapy • new therapies
- vaccine

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(Th-2) response. Hence, most new-generation epitopes for active A β -immunotherapy avoid this region of the peptide. Currently, three drugs are being assayed: the A β_{1-6} peptide coupled to the Q β coat protein (CAD106), a tetra-palmitoylated A β_{1-15} peptide liposome-based vaccine (ACI-24) and a combination of UBITH[®] helper T-cell epitope (activating Th-1 response, rather than Th-2) and A β_{1-14} (UB-311) [3]. CAD106 (Novartis, Basel, Switzerland) is in Phase II/III clinical trial, ACI-24 (AC Immune, Lausanne, Switzerland) in Phase I/II and UB-311 (United Neuroscience Ltd, Dublin, Ireland) in Phase II.

The main drawback of active immunotherapy is the difficulty of intervening whenever adverse effects occur. Passive immunotherapy, in other words, treating the patients with *ex vivo* produced monoclonal antibodies (mAbs), overcomes this problem. Eight A β -directed mAbs have been, or are being, tested in clinical trials: bapineuzumab, ponezumab, solanezumab, gantenerumab, crenezumab, aducamab, BAN2401 and SAR228810 [3].

In 2000 it was demonstrated that peripheral injection of a mAb specific for the A β_{1-5} peptide generated the transfer of antibody to the brain, the antibody binding to amyloid plaques and the induction of fragment-crystallizable region (Fc) receptor-mediated microglial phagocytosis of A β deposits in PDAPP mice [5]. Bapineuzumab (Janssen, NJ, USA and Pfizer, NY, USA), which recognizes all forms of the A β peptide, is the humanized successor of this antibody and has reached many Phase III clinical trials [6]. However, the occurrence of Amyloid-related Imaging Abnormalities (ARIA) denoting microhemorrhage, especially in the *APOE ɛ4* carrier cohorts, halted the study in 2012. Some Phase I clinical trials with a redesigned mAb intended to minimize the risk of ARIA were completed in 2014, but they did not achieve safety requirements and the company discontinued its development.

Ponezumab (Pfizer) is a humanized mAb designed to recognize the C-terminus A β_{30-40} peptide region, which allows the binding of the plasma A β peptide so that the hippocampal amyloid burden is diminished by efflux [7]. However, no improvement in cognitive impairment was observed in two completed Phase II trials and it was repurposed for treating cerebral amyloid angiopathy (CAA), with a Phase II trial ongoing [3].

Solanezumab (Eli Lilly and Co., IN, USA and Hoffmann-LaRoche, Basel, Switzerland) is

a humanized mAb directed to the A β_{16-24} mid-region and is able to bind plasma A β in PDAPP mice, so that A β deposits are also reduced by promoting A β efflux. In Phase I, nonadverse effects appeared and some biochemical markers changed. Following Phase II trials with higher doses, a Phase III trial among patients with mild AD showed 33% reduction in the rate of decline [8] and two other Phase III studies are ongoing [3]. However, it is worth mentioning that the benefit found to date is not better than that of the palliative acetylcholinesterase inhibitor drugs.

Gantenerumab (Hoffmann-La Roche) was the first fully human mAb for A β -immunotherapy. In a mouse model of AD, this mAb showed sustained binding to cerebral amyloid and reduced amyloid plaques by recruiting microglia and preventing new plaque formation, while plasma A β remained the same. Phase I clinical trials in mild-to-moderate AD patients reduced the brain amyloid load, but two patients experienced ARIA [9]. At this moment three trials are ongoing: a Phase III trial with patients in the prodromal phase, a Phase II/III with familial AD mutations carriers and a Phase III trial with mild AD patients [3].

Crenezumab (Genentech, CA, USA) is a humanized mAb against the A β_{12-23} mid-region that was designed on an IgG4 scaffold, instead of the IgG1 for other mAbs, to avoid inflammatory effects [10]. Interestingly, crenezumab and solanezumab are cross-reactive, although two amino acidic changes in their sequence lead to the recognition of different species, in other words, monomers by solanezumab and protofibrillar species by crenezumab. Phase I trials in mild-to-moderate AD patients presented a good safety profile and Phase II testing with higher doses has been continued into an open-label-extension trial that will run until 2017 [3].

Aducanumab (Biogen Idec, MA, USA) is a human IgG1 mAb derived from an AD patient with an unusually stable clinical course. It showed the reduction in amyloid burden by binding insoluble fibrillar A β in a mouse model. Similarly to bapineuzumab, aducanumab recognizes A β ’s N-terminal residues but also a conformational epitope featuring aggregated A β . In a Phase I clinical trial, patients with mild AD showed reduced cognitive decline and decreased brain levels of amyloid, although ARIA occurred in some cases [11]. Dose reduction for the subsequent Phase II trial proved safe and effective in amyloid clearance, but improvement in

mental decline was not achieved. Currently, two Phase III trials are recruiting participants [3].

BAN2401 (Eisai Inc., Tokyo, Japan) is a conformation-dependent humanized mAb directed against the APP Arctic mutation (E22G in A β), which recognizes a unique conformation in the A β protofibril. Phase I clinical trials showed no serious adverse events and a Phase II trial began in January 2013 among patients with MCI and early AD [12].

SAR228810 (Sanofi, Gentilly, France) is a humanized mAb, derived from an IgG4 subclass as in the case of crenezumab, that recognizes a repeating conformational epitope of prefibrillar A β aggregates [13]. A Phase I clinical trial with mild-to-moderate AD patients has recently been completed [3].

In summary, passive immunotherapy is more advanced than active immunotherapy but its drawbacks, such as the occurrence of ARIA, complicate its development. The main hypothesis for bapineuzumab's failure in clinical trials is that trial participants were in advanced stages of the disease. Consequently, most of the studies currently ongoing are being performed with patients at the prodromal or MCI stages. In this vein, three consortia are working on to prevent the disease developing: the Alzheimer's

Prevention Initiative (API), the Dominantly Inherited Alzheimer's Network (DIAN) and the Anti-Amyloid treatment in Asymptomatic Alzheimer's (A4). API tests crenezumab in individuals from a large Colombian family which carries an AD mutation; DIAN tests immunotherapy with solanezumab or gantenerumab in adult children of a parent with the same mutation; and, finally, A4 tests solanezumab in asymptomatic elderly patients with amyloid positive PET. Thus, although these studies will take several years, it can be concluded that immunotherapy shows glimmers of promise [14,15] and it is likely we are getting closer to finding a disease-modifying drug to treat this devastating disease.

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Financial & competing interest's disclosure

Instituto de Salud Carlos III/FEDER (FIS-PI113-01330), Generalitat de Catalunya (SGR-GRC-2014-00885) and Generalitat de Catalunya/FEDER (2014-PROD00032). PIF-UAB student grants (J Güell-Bosch, L Montoliu-Gaya and G Esquerda-Canals). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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