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Christoph Hock, Roger M. Nitsch

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Original Paper

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Christoph Hock   Roger M. Nitsch

Division of Psychiatry Research, University of Zurich, Zurich, Switzerland

Abstract

Clinical observations with AN-1792 using tissue amyloid plaque immunoreactivity (TAPIR) analyses established for the first time evidence in humans that antibodies against β-amyloid-related epitopes are capable of slowing progression in Alzheimer's disease. Antibodies derived upon TAPIR assay selection may specifically target the pathologic neoepitopes of aggregated Aβ species present in amyloid plaques and some of their aggregated, protofibrillar and low molecular weight oligomeric precursors. We briefly summarize here how the proof of concept was established and why it provides the basis for a potential cure for Alzheimer's disease.

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Introduction

The first immunization therapy of Alzheimer's disease (AD) which entered clinical study phases 1 and 2 in 2000 and 2001 was loaded with high expectations, since the previous experiments in transgenic mice had shown removal of brain β-amyloid plaques accompanied by functional restoration [1, 2]. However, soon after the start of the phase 2 study the public awareness was drawn to the occurrence of severe side effects in the form of aseptic meningoencephalitis in 6% of the patients on active vaccine. As a consequence, active dosing of the vaccine was halted, and further development was put on hold. Much criticism and pressure was put on the clinical investigators and also on the supporters of the amyloid cascade hypothesis. Seemingly, an exciting scientific and treatment opportunity had been about to get lost, but meticulous biological analyses and long-term clinical follow-up of the immunized patients ultimately revealed remarkable indications for efficacy and proof of concept – even after the occurrence of meningoencephalitis in individual patients. We briefly summarize here how the proof of concept was established and why it provides the basis for a potential cure for AD (table 1).

Generation of Antibodies against β-Amyloid Plaques in Patients with AD

The formulation of the first active vaccine against β-amyloid was composed of preaggregated, fibrillar, synthetic $A\beta_{42}$ peptides combined with QS-21 as an adjuvant. It was termed AN-1792. A clinical safety and tolerability phase 1 study was done, with single and multiple dosing of AN-1792 in AD patients, and immunogenicity was assessed in this trial as well [3]. The study was followed by a phase 2 multicenter trial in 372 patients to assess safety, tolerability and pilot efficacy of AN-1792 [4]. Within the

Christoph Hock
Division of Psychiatry Research, University of Zurich
August Forel Strasse 1
CH–8008 Zürich (Switzerland)
Tel. +41 44 384 2271, Fax +41 44 384 2275, E-Mail chock@bli.unizh.ch

Table 1. Active β-amyloid immunization status

Rationale in mice	Rationale in humans	Limitations
Reduction in amyloid plaques	Indications for reduced amyloid plaque load	Aseptic meningoencephalitis in humans
Restoration of memory	Better memory over time	Microhemorrhages in some transgenic mouse models
Microglial phagocytosis of amyloid	Indications for microglial phagocytosis of amyloid Indications for restoration of hippocampal volumes	Limited antibody responder rate Balancing of B cell versus T cell response

phase 2 study, we investigated a cohort of 30 patients in Zurich. We analyzed both the quality and the titers of antibodies against β-amyloid plaques generated in response to the vaccination. To analyze antibodies against pathologically relevant β-amyloid-related structures, we developed the tissue amyloid plaque immunoreactivity (TAPIR) assay. It enabled us to identify and to quantitate antibodies that are not always detected by conventional ELISAs. In contrast to ELISAs, with immobilized preparations of pure synthetic peptides, the TAPIR assay uses bona fide tissue β-amyloid plaques that had been deposited in vivo in living brains, that had been developing slowly over a long period of time, in close contact to neuropil proteins as well as with neurite membranes, reactive astrocytes and activated glial cells. We expected that these conditions would allow for the detection with high sensitivity of pathologically relevant, aggregated Aβ species neoepitope conformations including low molecular weight oligomers, protofibrils and fibrils. If low molecular weight oligomers, protofibrils and fibrils are relevant immunotherapeutic targets, TAPIR assays should be suitable for detecting biologically relevant immune responses. In fact, we found significant increases in serum titers of TAPIR-positive antibodies in the vast majority of the 30 patients in the Zurich subcohort of the phase 2 AN-1792 trial [5]. In line with our considerations, this group of patients was not identical to the group of patients with increased ELISA titers: Several patients in the Zurich cohort had increases in TAPIR-positive antibodies in the absence of an ELISA-positive immune response, and vice versa, pointing to the difference in epitopes presented by ELISAs versus TAPIR assays [6]. Since studies in transgenic mice had raised the possibility of antibody passage from blood to brain over the blood brain barrier [7], we analyzed CSF samples obtained before and after immunization and found that the TAPIR-positive IgG antibodies were indeed present in CSF. This was true for CSF obtained from patients both with and without signs of blood-brain barrier dysfunction. Thus we showed that antibodies against β-amyloid-related epitopes were able to cross the blood-brain barrier and, presumably, reached the therapeutic targets in the brain. The mechanisms for blood-brain barrier passage of plasma-derived IgG are incompletely understood. They may include increased blood-brain barrier permeability, possibly related to disease- or vaccination-induced inflammatory responses, passive diffusion, and active shuttling, possibly via F_{cN}-mediated transcytosis.

Antibodies against β-Amyloid-Related Epitopes Slowed AD Progression

To explore the predictive value of antibody generation on the clinical outcome over time, we analyzed the Zurich subcohort of 30 patients using the TAPIR assay in serum pre- and postimmunization. We found that both cognitive functions and capacities of daily living declined less in patients with increased serum titers of TAPIR-positive antibodies as compared to patients without such antibodies [6]. Moreover, there was a correlation of the antibody titers with clinical outcome. Patients with higher TAPIR scores showed better clinical performance over time, and the group of patients with the highest TAPIR scores remained cognitively and functionally (on the basis of daily living capacities, DAD scale) stable for the entire observation period of 1 year. Interestingly, the titers of antibodies also remained increased throughout this time period. Interestingly, the clinical analysis of the phase 1 study in 80 patients also indicated positive effects on the level of daily living capacities as measured by the DAD scale [3]. The clinical analyses of the multicenter cohort of 372 patients confirmed our observations by demonstrating better performance of antibody responders identified by peptide-based ELISAs in a number of neuropsy-

chological test batteries [4]. TAPIR analyses done in the entire cohort of 372 patients yielded similar results, thus confirming the positive effects of β-amyloid immunization on memory performance in patients with AD [Hock, et al., in preparation]. Together, these clinical analyses of the first studies using β-amyloid immunization suggest that antibodies against β-amyloid-related epitopes are effective in slowing progression of dementia in AD.

Neuropathological Indications for β-Amyloid Removal from Brain

Neuropathological investigations of 3 patients immunized with AN-1792 showed reduced β-amyloid pathology in extended brain areas along with lowered astrogliosis, while presence of neurofibrillary tangles appeared to be preserved [8–10]. Importantly, removal of β-amyloid was observed both in presence and absence of prior episodes of meningoencephalitis or signs of T cell infiltration of the brain. These findings suggest that meningoencephalitis is not required for β-amyloid removal. The presence of microglia filled with β-amyloid in brain areas that have been cleared from β-amyloid following immunotherapy indicated that phagocytosis of β-amyloid by microglial cells may constitute an important mechanism of plaque removal from brain [8, 10]. Additional mechanisms may include peripheral amyloid sink and antibody-mediated disaggregation which may finally add to amyloid clearance.

Effects of Antibodies against β-Amyloid-Related Epitopes on Hippocampal Volumes Measured by MRI

MRI-based analysis of brain volumes revealed interesting longitudinal changes which were different in patients with antibodies against β-amyloid-related epitopes and those without such antibodies. Fox et al. [11] analyzed the multicenter cohort and observed a stronger decrease in brain volumes including the hippocampus in patients with antibody response as compared to patients without antibody response within 1 year of observation. This finding was interpreted as an effect of lowered β-amyloid plaque load and reduced inflammation and astrogliosis. In our own independent analysis of the Zurich cohort of 30 patients we also observed the greater hippocampal volume loss in patients with antibodies against β-amyloid during the first year of clinical observation, as compared to patients without such antibodies. In contrast to the mul-

ticenter cohort, however, we continued the clinical follow-up investigations including the MRI scanning over a period of 2 years. During the second year of clinical follow-up the hippocampal volumes restored in the patients with antibodies against β-amyloid-related epitopes and returned close to the baseline volumes [Hock et al., in preparation]. In contrast, the hippocampal volumes in patients without antibodies against β-amyloid-related epitopes continued to decrease at the expected rate of roughly 3% per year. These results raise the fascinating speculation of a biphasic process of regeneration; first, an initial volume loss reflecting β-amyloid plaque removal and concurrent loss in astrocyte activation; second, a phase of structural build-up and volume restoration as signs for recovery and regeneration. Combined with MRI volumetry, amyloid PET imaging will allow for addressing this possibility during the upcoming clinical immunotherapy trials [12].

Conclusions

Clinical observations with AN-1792 using TAPIR analyses established for the first time evidence in humans that antibodies against β-amyloid-related epitopes are capable of slowing AD progression. Antibodies derived upon TAPIR selection may specifically target the pathologic neoepitopes of aggregated Aβ species present in amyloid plaques and some of their aggregated, protofibrillar and low molecular weight oligomeric precursors. Thus, such antibodies may specifically reduce the neurotoxicity related to neoepitope formation. Since the formation of abnormally aggregated Aβ species occurs early in the disease process leading to AD, prevention of its formation or its removal may be expected to result in the slowing or the prevention of neurodegeneration. Possibly, the successful reduction in Aβ-related toxicity may also ameliorate such down-stream effects as inflammation, oxidative stress, cytoskeletal abnormalities, the formation of neurofibrillary tangles, synaptic dysfunction, deficits in neurotransmission and homeostasis of ions and metabolism. If clinical safety and tolerability can be improved, the collected evidence reported here supports strongly that immunotherapy directed against toxic Aβ species in brains holds the promise of a future cure for AD.

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