alzheimer's research&therapy

COMMENTARY

Can novel therapeutics halt the amyloid cascade?

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Abstract

The amyloid hypothesis provides a basis for the development of new therapeutic strategies in Alzheimer's disease. Two large trials have recently been published. The first is a phase 2 study of passive immunotherapy with bapineuzumab, a humanized anti-Aβ monoclonal antibody directed against the N-terminus of Aβ. This trial showed no differences within dose cohorts on the primary efficacy analysis. Exploratory analyses showed potential treatment differences on cognitive and functional endpoints in study completers and apolipoprotein E ε4 noncarriers. A safety concern was the occurrence of reversible vasogenic edema. The second study is a phase 3 trial of tarenflurbil, a modulator of the activity of γ-secretase. Tarenflurbil had no beneficial effect on the primary or secondary outcomes. The tarenflurbil group had a small increase in frequency of dizziness, anemia, and infections. Possible explanations for the negative results of these trials may be related to the study design or the choice of dosage. However, it may also be that these negative findings reflect our still incomplete understanding of, at least part of, the pathogenesis of Alzheimer's disease.

Introduction

Despite a significant increase in our understanding of the pathogenesis of Alzheimer's disease (AD) over the past two decades, the therapeutic options are still very modest. Cholinesterase inhibitors and the N-methyl-D-aspartate receptor agonists currently available have a modest clinical effect but do not intervene with the underlying pathophysiology [1]. The ultimate aim of AD therapy is to stop or slow down the underlying disease process.

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Recently the first two large trials with drugs that may slow disease progression have been published: a phase 2, passive immunization trial with bapineuzumab; and a phase 3 trial with tarenflurbil, a modulator of γ-secretase. Both drugs supposedly interfere with β-amyloid (Aβ) metabolism. Abnormalities in Aβ processing are thought to be central in AD pathophysiology according to the amyloid cascade hypothesis. The mode of action of bapineuzumab is to remove aggregated Aβ, while tarenflurbil decreases the production of the pathogenic Aβ42 peptide. In the present commentary, we discuss the results of these trials and the implications for future therapy and insight into AD pathophysiology.

The amyloid cascade

The amyloid hypothesis has led to an understanding of the pathology of AD, and also provides a basis for novel drug development. This hypothesis suggests that increased Aβ42 production and subsequent aggregation in limbic and association cortices leads to synaptic changes and causes deposition of Aβ42 in diffuse plaques, which in turn causes microglial and astrocytic activation. As a result, altered neuronal homeostasis and oxidative injury lead to tangle formation, and eventually to neuronal and synaptic dysfunction and selective neuronal loss [2,3]. The most important implied prediction of the hypothesis is that reduction of Aβ aggregation would ameliorate AD symptoms.

Three methods for intervening in the amyloid cascade have thus far been tested in clinical trials: active immunization, passive immunization, and modulation of γ-secretase [4,5]. In this light we shall discuss the two recent clinical trials mentioned above: the phase 2 trial with bapineuzumab, and the phase 3 trial with tarenflurbil.

Bapineuzumab

Bapineuzumab is a humanized anti-Aβ monoclonal antibody. Preclinical passive immunotherapy studies with monoclonal anti-Aβ antibodies in a mouse model of AD showed antibody binding to Aβ plaques, reduction in Aβ plaque burden, and reversal of memory defects [6,7]. Bapineuzumab is directed against the N-terminus of Aβ and is hypothesized to bind to Aβ in the brain and to facilitate its removal.

The recently published phase 2 multiple-ascending-dose trial in mild to moderate AD tested the safety and efficacy of bapineuzumab [8]. Two hundred and thirty-four AD patients were randomly assigned to intravenous bapineuzumab (n = 124) or to placebo (n = 110) in four dose cohorts (0.15, 0.5, 1.0, or 2.0 mg/kg). Patients received six infusions, 13 weeks apart, with final assessments 18 months later. The primary efficacy analysis compared treatment differences within dose cohorts on the Alzheimer's Disease Assessment Scale for Cognition and on the Disability Assessment for Dementia. No significant differences were found in the primary efficacy analysis.

Exploratory analyses, however, showed potential treatment differences on cognitive and functional end-points in study completers and apolipoprotein E (APOE) ε4 noncarriers. In this subgroup, subjects on active treatment showed 5 points less decline on the Alzheimer's Disease Assessment Scale for Cognition after 78 weeks compared with placebo. A safety concern was the occurrence of reversible vasogenic edema, detected on brain magnetic resonance imaging in 10% of the bapineuzumab-treated patients. Vasogenic edema was more frequent in APOE ε4 carriers, which may suggest that vasogenic edema is related to vascular amyloid burden since APOE ε4 carriers show more vascular amyloid deposition.

The potential treatment differences in the exploratory analyses have led to the evaluation of bapineuzumab in a phase 3 trial that started in December 2007, which will take possible treatment differences by APOE ε4 status into consideration. Meanwhile, a recent publication showed that treatment with bapineuzumab for 78 weeks reduced fibrillar amyloid burden in subjects with AD, shown by Pittsburgh compound B positron emission tomography ((PiB-PET) [9].

Tarenflurbil
Tarenflurbil is a modulator of the activity of γ-secretase, and may for that reason act as an Aβ42 lowering agent. In mouse models of AD, tarenflurbil prevents learning and memory deficits and reduces Aβ42 brain concentrations [10]. In an earlier phase 2 trial in 210 AD patients, mildly affected patients (baseline mini-mental state examination 20 to 26), who received 800 mg tarenflurbil twice per day, had lower rates of decline in activities of daily living and global function compared with subjects who received placebo [11].

These results led to a large multicentre, phase 3, randomized, double-blind, placebo-controlled trial for the evaluation of the efficacy, safety, and tolerability of tarenflurbil in 1,684 subjects with mild AD (mini-mental state examination 15 to 26) [12]. Initially, patients were assigned to treatment with tarenflurbil at doses of either 400 or 800 mg twice daily or placebo. After an analysis of

phase 2 data indicated that subjects had the strongest response to 800 mg tarenflurbil twice daily, however, the 400 mg dose was ended. The main outcome measures were the change from baseline to 18 months score on the Alzheimer's Disease Assessment Scale for Cognition and on the Alzheimer's Disease Cooperative Study – Activities of Daily Living scale. Tarenflurbil had no beneficial effect on the primary or secondary outcomes. The APOE genotype had no effect on treatment response. The tarenflurbil group had a small increase in frequency of dizziness, anemia, and infections.

Discussion
What have these two trials taught us? The bapineuzumab trial showed that intravenous administration of the serial bapineuzumab doses is feasible and, as long as the possible occurrence of vasogenic edema is monitored, is relatively safe. The positron emission tomography substudy provided the suggestion that bapineuzumab indeed reduces amyloid load *in vivo*. The lack of effect on the primary endpoint of the trial may be due to the fact that, as the authors point out, it was underpowered to show small differences in efficacy. Indeed, a larger sample size would have increased the ability to detect statistically significant differences, but this does not alter the notion that clinical effects may still be small and of limited relevance. In the case of the tarenflurbil trial, it is possible that the dose of 800 mg twice daily was still too low. The discrepant findings between the phase 2 subgroup analyses and the phase 3 study strongly caution against apparent overinterpretation of *post hoc* analyses.

The findings may also have implications for the amyloid hypothesis. First, it is possible that the relation between amyloid processing and AD is modified by the APOE genotype, and in this respect it will be interesting to see how a possible treatment effect may differ by APOE ε4 status in the new phase 3 bapineuzumab study. It stresses again how important APOE is in several aspects of AD [13,14].

Second, as reduction of Aβ42 was not effective and removal of aggregated Aβ had a limited effect, other Aβ species may be the main toxic agent in AD or the AD pathology may not depend on Aβ. Alternative models for AD pathophysiology may better explain how accumulation of Aβ42 leads to tangle formation, and why tangle formation is closer to neuronal cell death than amyloid accumulation [2].

Third, reduction of Aβ production or removal of Aβ may not be successful in patients who already have a substantial amyloid burden if the cascade becomes independent of amyloid burden once Aβ42 accumulation has set off an irreversible chain of events.

Finally, the amyloid hypothesis neglects the role of cerebrovascular damage, which is typically comorbid in

older patients with AD, and may be a crucial cofactor in causing neurodegeneration and may interact with the pathology of AD [15]. Cerebrovascular damage is a factor that may have to be taken into account when developing new therapeutic strategies for AD.

Abbreviations
Aβ, β-amyloid; AD, Alzheimer's disease; APOE, apolipoprotein E.

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