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Therapeutic news in Alzheimer's disease: soon a disease-modifying therapy?

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Abstract: Research on disease-modifying treatments for Alzheimer’s disease has resulted in a series of failures over the past 20 years. However, in the last three years, four molecules have shown significant effects on clinical endpoints in phase II or III clinical trials (i.e., slowing of cognitive decline). Among these four molecules, 3 are anti-amyloid immunotherapies: aducanumab, donanemab, and lecanemab, responsible for a significant clearance of cerebral beta-amyloid deposits. These provisional data are still awaiting confirmation to put an end to the controversy surrounding the 2021 Food and Drug Administration’s decision to give conditional approval to aducanumab, which is considered premature by many specialists. Confirmation is also necessary to assess the benefit (magnitude of the slowing of cognitive decline) and risk (edema and cerebral hemorrhage induced by these treatments) balance of these molecules. Masitinib, a treatment whose probable mechanism of action is neuroinflammation, has also shown positive effects that need to be confirmed. Therapies targeting the tau protein are less advanced and have yet to be proven. Patients have renewed hope since it may not be unreasonable that these disease-modifying therapies will be part of the French therapeutic arsenal within the next five years.

Keywords: Alzheimer’s Disease / Amyloid beta-Peptides / Passive Immunization / Drug Therapy
The pharmacopeia for Alzheimer's disease has not evolved in the last 20 years and has remained limited only to symptomatic treatments. It even took a step backward in 2018 with the delisting of anticholinesterase drugs. Nevertheless, numerous research projects continue to be carried out, focusing on the pathophysiological mechanisms of the disease, to develop a disease-modifying treatment. We propose to summarize the recent results of the most promising therapeutic trials (i.e., showing significant results on clinical criteria in the most advanced phases of development) concerning potential disease-modifying treatments for Alzheimer's disease. This review is not intended to be exhaustive, as 104 possible disease-modifying therapies for Alzheimer's disease are currently being evaluated in humans [1].

1. Treatments targeting the amyloid pathway

In the 1990s, the discovery that the genes responsible for the monogenic forms of Alzheimer's disease are uniquely located in the amyloid metabolic pathways, focused research on the amyloid pathway. This, coupled with numerous fundamental studies, has led to the amyloid cascade hypothesis, according to which the primum movens of the pathophysiology of Alzheimer's disease is amyloid pathology [2]. The most credible short-term therapeutic hopes still rest on this hypothesis. The first therapeutic trials targeting the amyloid protein appeared in the early 2000s through vaccination. Unfortunately, these trials had to be stopped prematurely due to meningoencephalitis [3]. Trials with passive immunotherapies resumed in the late 2000s with numerous failures. All clinical trials with anti-amyloid antibodies were negative on clinical criteria [4]. The latest failure is the DIAN-TU trial, testing the efficacy of two anti-amyloid monoclonal antibodies: gantenerumab and solanezumab, in asymptomatic or mildly cognitively impaired patients with autosomal dominant Alzheimer’s disease [5]. Hopes for a disease-modifying therapy targeting the amyloid pathway were diminishing, not to mention the failure of inhibitors of the amyloid precursor peptide (APP) enzymes (beta- and gamma-secretases), some of which aggravated cognitive impairment [6]. Several analyses
and lessons have been drawn: the first is theoretical, questioning the hypothesis of the amyloid cascade in sporadic Alzheimer's disease; the other is methodological, criticizing the target populations, doses, and pharmacodynamic effect in the trials. Theoretical criticisms are mainly based on the lack of correlation between amyloid pathology and patient symptomatology: cross-sectional studies show the absence or a very weak correlation either in vivo (measured by positron emission tomography - PET) or post-mortem, in contrast to tau pathology, which is very well correlated with symptoms [7][8]. Moreover, the onset of tau pathology is consistent with age and precedes that of amyloid pathology in large neuropathological cohorts [9]. More recent longitudinal cohort data have also shown that individuals over 60 years old without cognitive impairment and with significant amyloid pathology have a less than 50% lifetime risk of developing symptoms of Alzheimer's disease [10] and have no or only minimal short term acceleration of tau pathology [11]. In light of these observations, alternative models have recently emerged that challenge the amyloid cascade hypothesis [12]. They propose a probabilistic model (tau and amyloid pathologies would appear independently under the accumulation of multiple risk factors) rather than deterministic [12].

Regarding methodological criticisms, the first trials were conducted on patients without searching Alzheimer's disease pathology biomarkers. However, it is now known that approximately one-third of patients with Alzheimer's type dementia do not have Alzheimer's pathology [13]. Naturally, suppose a treatment is aimed at amyloid pathology, and a third of the patients tested do not have amyloid pathology. In that case, this will alter the ability of the trial to show an effect. Moreover, these trials were also initially conducted in patients with moderate or advanced stages of the disease. We also know that because of its pathological effect, theoretically very upstream according to the amyloid cascade hypothesis, the influence of amyloid pathology is probably not very important once the disease is advanced (where tau pathology and neurodegeneration are then the most determining factors). Following these criticisms, the trials continued targeting patients at earlier stages with evidence of underlying amyloid pathology, but the failures continued [14–16].
In 2016, the results of the Phase Ib study (PRIME) of aducanumab were published, which had the effect of a small revolution in the field [17]. This trial was indeed the first to show (even if this type of trial is not designed to do so) a significant clinical effect (slowing of clinical decline on a hybrid scale measuring cognitive impairment and its functional impact: the Clinical Dementia Rating scale - CDR) in a dose-dependent manner on anti-amyloid immunotherapy after 12 months of treatment.

So how is aducanumab different from other anti-amyloid immunotherapies that have all failed? The answer is probably pharmacodynamic: aducanumab not only prevents the accumulation of insoluble amyloid deposits but also leads to a significant clearance of these deposits (even negativ ed amyloid PET) when other immunotherapies did so only slightly or specifically targeted toxic soluble amyloid species (oligomers) without modifying the amyloid load (i.e., the insoluble deposits measured by amyloid PET). Since then, several signals have continued to emerge in this direction. First, the twin phase III studies of aducanumab (EMERGE and ENGAGE) show ambiguous but encouraging results (unpublished data; [18]). One trial was positive (EMERGE), and another trial was (frankly) negative (ENGAGE) on the primary clinical endpoint (slowing of cognitive decline measured by the CDR scale). This is insufficient by the usual standards for marketing authorization, but subgroup analyses and analyses of biomarkers of tau pathology suggest that a clinical effect may be emerging [19]. In addition, two other anti-amyloid antibodies responsible for high clearance of amyloid deposits have shown positive phase II trials results on clinical endpoints: lecanemab and donanemab [20,21]. Somehow, these data can be seen as external confirmation of the ambiguous aducanumab results.

The magnitude of the effect of these three antibodies on the slowing down of cognitive decline seems to be mild to moderate for the moment. To illustrate quantitatively this 'mild to moderate' effect with a cognitive test widely used in France, in the positive phase III trial of aducanumab (EMERGE), the high dose group (the only one to be effective) lost on average 2.7 points of MMSE in 18 months when the placebo group lost 3.3 points. Given the mode of action of these drugs, this effect can also be expected to persist over time as suggested by the 4-year follow-up effects of the PRIME study (i.e., an estimated 4-point difference in MMSE at ten years between the placebo and
treated groups) [22]. The downside of these antibodies is the increase in an adverse effect observed since the appearance of anti-amyloid immunotherapies: ARIAs (amyloid-related Imaging Abnormalities). ARIAs come in two forms: edematous (ARIA-E) and hemorrhagic (ARIA-H) and are similar to cerebral amyloid angiopathy-related inflammation [23]. In most cases, they are benign (simple headaches) or asymptomatic (discovered during the systematic MRI monitoring performed in the various trials) and disappear with the temporary cessation of infusions. Nevertheless, the increase in amyloid clearance generated by the molecules tested in the most recent trials has increased their frequency (35% of ARIA-E and 28% of ARIA-H in the phase 3 trials of aducanumab) but also the severity of these ARIA [24]. Therefore, this point will be critical to monitor and quantify in future trials.

2. Treatments targeting the tau pathway

Because tau pathology is better correlated with patient symptoms, treatments targeting this pathway also hold great promise. The main pharmacological class of therapies targeting tau pathology is immunotherapy (directed against the tau protein). Given the essentially intracellular localization of tau pathology, the mechanism of action of these immunotherapies is probably not identical to that of anti-amyloid immunotherapies (leading to complete clearance of hyperphosphorylated tau protein). Although not perfectly known, it probably acts by limiting the tau protein’s trans-synaptic propagation, demonstrated in recent years [25]. Indeed, given the intracellular target of pathological forms of tau, it is unlikely that antibodies will act on already aggregated intracellular forms. Although promising from a theoretical point of view, the first signals emerging from these trials are for the moment weak and ambiguous: two phase II clinical trials were prematurely stopped this year for futility (semorinemab, TAURIEL trial - in patients with mild Alzheimer’s disease, and gosuranemab, TANGO trial), while the AC Immune® company communicated at the end of August 2021 that their other phase II trial for semorinemab was
showing positive results (LAURIET trial - in patients with moderate Alzheimer's disease). Three other passive anti-tau immunotherapy trials are still ongoing (JNJ-63733657, tilavonemab, zagotenemab). Active immunotherapy trials (vaccines) are also underway, with some hope raised by very preliminary results from a phase II trial (small size, post hoc analysis, etc.) [26].

3. Treatments targeting other pathways

Another positive signal also emerged from a less common pathway, the brain innate immune system, with the results of the phase II trial of masitinib (press release - unpublished data). Masitinib is a small molecule tyrosine kinase inhibitor targeting inflammation pathways (mast cells and macrophages/microglia: c-Kit, Lyn, Fyn, and CSF1R kinases). Its mode of action would be inhibition of mast cell activity (which could influence neuroinflammation and regulation of blood-brain barrier permeability) and inhibition of the Fyn protein kinase, which has a role in amyloid signaling and tau phosphorylation [27]. This treatment was initially developed in mastocytosis and is currently being tested in many neurological and non-neurological diseases. The trial showed at five months a significant decrease of 1.51 points on the ADAS-Cog cognitive scale in the treated group (n = 182) when the placebo group worsened its performance by 0.63 points. Patients included in the trial had a MMSE between 12 and 25 and a diagnosis of Alzheimer's disease without the use of biomarkers. A phase III trial is underway to confirm these results.

4. Conclusion

This is a first in the field of Alzheimer's disease: four phase II and III clinical trials concerning possible disease-modifying therapies have been positive over the last three years. The high-dose anti-amyloid immunotherapies in patients with biologically proven mild Alzheimer's disease seem to consistently demonstrate the beginning of efficacy in slowing cognitive decline. These data must, of course, be
confirmed. From a legislative point of view, aducanumab is the most advanced treatment as it was granted conditional approval by the Food and Drug Administration on June 7, 2021. This approval does not presume the clinical efficacy of the drug. Still, it considers its biological effectiveness (reducing amyloid deposits) to be sufficient in the image of the procedures often used in oncology to accelerate the availability of drugs for severe diseases with no therapeutic alternative [19]. The company will conduct a new large and global phase III randomized-control trial starting this year to resolve the ambiguity of the results obtained with EMERGE and ENGAGE clinical trials. Its results are expected in 2026. Nevertheless, this decision is highly controversial in the literature, notably because the decrease in amyloid load has never been proven to be a valid surrogate marker for judging possible clinical efficacy (whereas in oncology, tumor growth or the number of metastases are validated markers) [28]. Conversely, the European Medicines Agency refused the approval of aducanumab on December 16th 2021. Biogen® appealed this decision, and it is currently being re-examined. As for the other molecules, the results of phase III trials are not expected before the beginning of 2023 for lecanemab and in 2024 for donanemab. Therefore, it is no longer unreasonable to imagine having a disease-modifying treatment available in clinical practice for Alzheimer’s disease in the next five years. Hope for patients is reborn!

References


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