Immune-based pharmacotherapy for Alzheimer's disease: Aβ-targeting monoclonal antibodies.

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En la actualidad no se dispone de ningún fármaco protector o regenerador neuronal para la enfermedad de Alzheimer (EA), reconocida como un grave peligro para la salud que afecta sobre todo a personas mayores de 60 años. La investigación reciente sobre la EA se ha centrado en explorar algunos rasgos distintivos de la enfermedad, como la neuroinflamación y la hiperexcitabilidad central.

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RESUMEN

En el presente artículo se analizan los efectos terapéuticos y los resultados de los ensayos clínicos de los anticuerpos monoclonales aducanumab, lecanemab y donanemab en pacientes con enfermedad de Alzheimer (EA), así como el impacto en la patología y los perfiles clínicos de la EA.

Palabras clave: microglía, anticuerpos monoclonales, enfermedad de Alzheimer

ABSTRACT

The therapeutic effects and clinical trial results of monoclonal antibodies aducanumab, lecanemab and donanemab in patients with Alzheimer disease (AD) and the impact on AD pathology and clinical profiles are discussed on the present article.

Key words: microglia, monoclonal antibodies, Alzheimer disease

1. INTRODUCTION

The idea of the involvement of the brain's immune system in neurodegenerative disease, namely Alzheimer's disease (AD), is now already well established. The studies from Heneka *et al*. (2013) have cast light on the role of microglial cell proteins and how they recruit other cells to help clean up the brain from some inflammatory insults. Authors have described that microglial proteins are able to connect to the inflammasome, a complex sensor of danger signals. In AD, amyloid-β peptide (Aβ) activation of the NLRP3 inflammasome protein in microglia is fundamental for interleukin-1β maturation and subsequent inflammatory events. In their experiments Heneka *et al*. used *Nlrp3(–/–)* or *Casp1(–/–)* knock out mice because a prior association to some symptoms and signals for AD carried by them was reported and it has been demonstrated that they are protected from loss of spatial memory and other consequences associated with AD. The results showed reduced brain caspase-1 and interleukin-1β activation in addition to enhanced Aβ clearance which allowed the authors to conclude that the NLRP3/caspase-1 axis has a

pivotal role in the pathogenesis of AD, and to suggest that NLRP3 inflammasome inhibition in microglia might be a pharmacological target for the treatment of AD. Furthermore, the research leaded by Johnsson *et al.* (2013) in Icelandic people has identified a mutation in the gene encoding triggering receptor expressed on myeloid cells2 (*TREM2*), which has previously been associated with an autosomal recessive form of early-onset dementia. Their experimental protocols were based on a genome analysis with variants that were likely to affect protein function. From their results they found a significant correlation between the uncovered mutations and the risk of developing AD in Icelanders. Still, the investigation by Guerreiro *et al.* (2013) employed genome sequence techniques to analyse the genetic variability in *TREM2* in patients with AD and in controls. They found significantly more variants in exon 2 of TREM2 in patients with AD than in controls. Therefore, there no longer seem to be doubts that dysfunctions in microglia are closely involved in the pathogenesis of AD. Actually, according to Venegas *et al.* (2017), in mice, activated microglia are able to throw away inflammasome vestiges that in their turn can start new Aβ clusters, spreading the disease over the brain, as they have pointed out: "Toxic amyloid-β promotes inflammation, which promotes more toxic amyloid-β".

However, although a close correlation between inflammasome activation by microglia and brain disease is established (Salters and Stevens 2017) and perhaps new strategies for therapeutic approaches in pathologies like AD have emerged from that, some scientists have seen some practical problems in the run for an efficient drug to treat AD. In basic research, inadequate animal models might spoil a project; in clinical trials, recruiting early patients is also difficult (Abbott, 2018). Besides that, a lack of racial diversity in AD trials is also another critical issue that may give rise to plenty of doubts and possible failures in trial results (Reardon, 2023).

Nevertheless, even though the lack of a viable animal experimental model is still a barrier, the findings in the last few years can not impair a kind of optimism for the putative employment of immune-based pharmacotherapy for AD. In fact, some Aβ-targeting monoclonal antibodies have already been approved by the Food and Drug Administration (FDA), which bind different stages in the Aβ aggregation cascade. Thus, considering that Aβ aggregation triggers a cascade of pathophysiologic events, such as synaptic and network dysfunction, neuroinflammation, and the aggregation and spread of P-tau tangles, which culminate in cognitive decline and dementia, monoclonal antibodies by binding to Aβ aggregates may remove them from the brain. Therefore, the drugs can reduce the progress of the disease, namely the devastating cognitive impairment.

2. ADUCANUMAB

Aducanumab is a recombinant human monoclonal antibody that selectively targets Aβ peptide aggregates, being the first FDA-approved drug (2021) to directly modify a core molecular feature of AD pathophysiology. Clinical trials have demonstrated that treatment with aducanumab reduces brain Aβ plaques, an action accompanied by a dose-dependent slowing of clinical decline. The company Biogen has funded two randomized, double-blind, placebo-controlled, global, phase 3 studies of aducanumab (EMERGE and ENGAGE) to assess its efficacy and safety in patients with early AD (mild cognitive impairment [MCI] due to AD and mild AD dementia) (Haeberlein *et al.*, 2022). Participants included 1638 (EMERGE) and 1647 (ENGAGE) patients (aged 50–85 years, confirmed amyloid pathology) who met clinical criteria for MCI due to AD or mild AD dementia, of which 1812 (55.2%) completed the study. Participants were randomly assigned 1:1:1 to receive low-dose aducanumab (3 or 6 mg/kg target dose), high-dose aducanumab (10 mg/kg target dose), or placebo via IV infusion once every 4 weeks over 76 weeks. The primary outcome measure was a change from baseline to week 78 in the Clinical Dementia Rating Sum of Boxes (CDR-SB). The authors have reported the following results:

"EMERGE and ENGAGE were halted based on futility analysis of data pooled from the first approximately 50% of enrolled patients; subsequent efficacy analyses included data from a larger data set collected up to futility declaration and followed prespecified statistical analyses. The primary endpoint was met in EMERGE (difference of –0.39 for high- dose aducanumab vs placebo [95% CI, –0.69 to –0.09; P=.012; 22% decrease]) but not in ENGAGE (difference of 0.03, [95% CI, –0.26 to 0.33; P=.833; 2% increase]). Results of biomarker substudies confirmed target engagement and dose-dependent reduction in markers of Alzheimer's disease pathophysiology. The most common adverse event was amyloid-related imaging abnormalities-edema."

The authors concluded that the EMERGE high-dose aducanumab group met all primary and secondary endpoints. EMERGE was regarded as the first phase 3 trial to demonstrate an association between the reduction of biomarkers of AD pathology and a statistically significant slowing of clinical decline.

In fact, the EMERGE and ENGAGE aducanumab trials have found some controversial results that were reported by many researchers who complained about the analysis of the results and conclusion as well the accelerated approval by the FDA (Rabinovici, 2021). Even the authors have pointed out some limitations of the studies such as, for instance, a lack of diversity, including racial/ethnic diversity in the populations studied, as well as patients with co-morbid conditions, and those on some concomitant medications. For example, the main dose-limiting adverse effect associated with aducanumab is amyloid-related imaging abnormalities (ARIA), including imaging abnormalities due to vasogenic edema (ARIA-E) and intracranial haemorrhage (ARIA-H). In clinical trials, ARIA occurred in 41% of patients receiving the target dose of 10 mg/kg compared to 10% of those receiving

placebo (Haeberlein *et al*., 2020; Kandelshein and Bloemer, 2022). This complication raises worries about real-world safety.

3. LECANEMAB

The second Aβ-targeting monoclonal antibody approved by the FDA was lecanemab, a humanized immunoglobulin G1 (IgG1) monoclonal antibody, that preferentially targets soluble aggregated Aβ (Swanson *et al*., 2021). An 18-month, multicentre, double-blind, phase 3 trial (Clarity AD; supported by Eisai (regulatory sponsor), with partial funding by Biogen) involving persons 50 to 90 years of age with early AD (MCI or mild dementia due to AD) with evidence of amyloid on positron emission tomography (PET) or by cerebrospinal fluid testing based on Aβ PET lowering in a phase 2 study, was conducted to determine the safety and efficacy of lecanemab in participants (van Dyck *et al.* 2023).

The study's experimental design included random assignment of participants in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline to 18 months in the score on the CDR-SB (range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).Biomarker assessments included CSF biomarkers (Aβ1–40, Aβ1–42, total tau, phosphorylated tau 181 [p-tau181], neurogranin, and neurofilament light chain [NfL]) and plasma biomarkers (Aβ42/40 ratio, p-tau181, glial fibrillary acidic protein [GFAP], and NfL). The authors have reported the following results:

"A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, –0.45; 95% confidence interval [CI], –0.67 to –0.23; P<0.001). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference,–59.1 centiloids; 95% CI, –62.6 to –55.6). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, –1.44 (95% CI, –2.27 to –0.61; P<0.001); for the ADCOMS, –0.050 (95% CI, –0.074 to –0.027; P<0.001); and for the ADCS-MCI-ADL score, 2.0 (95% CI, 1.2 to 2.8; P<0.001). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%. "

Although the authors considered that in almost all studied parameters lecanemab was able to cause a reduction or inhibition of AD markers, concerns about ARIA cannot be neglected. The authors reported that in the lecanemab group, the incidence of ARIA-E was 12.6%, and the incidence of ARIA-H was 17.3%. These values are numerically lower than those in similar clinical trials although differences in trial design do not allow direct comparisons. The authors understood that the occurrence of ARIA may have caused participants and investigators to be aware of the trial-group assignments; therefore, they tried to minimize this putative bias by making clinical raters unaware of the safety assessments and the trial-group assignments. They performed sensitivity analyses to examine the effect of ARIA on clinical outcomes and reported that ARIA had no effect on the results. Other limitations of the study included having results for only 18 months of treatment; the trial was conducted during the COVID-19 pandemic and encountered obstacles including missed doses, delayed assessments, and intercurrent illnesses. The authors performed a sensitivity analysis that showed that the missed doses were consistent with the primary end-point analysis. In conclusion, the results allowed them to infer that in persons with early AD, lecanemab reduced brain amyloid levels that was associated with moderately less decline in clinical measures of cognition and function than placebo at 18 months but was associated with adverse events. However, they also pointed out that longer trials are necessary to determine the efficacy and safety of lecanemab in early AD. For example, it is unclear what impact the trial results will have on the lives of people with AD or even how long the effects will persist. Furthermore, three people who had been enrolled in the lecanemab phase III study died during the extended phase of the trial. Some researchers have regarded the deaths as being due to complications such as brain bleeding and seizures from lecanemab use (Piller, 2022), although the sponsors have not confirmed it. Scientists believe that the antibody weakened blood vessels in the brain as it attacked the amyloid plaques; also, considering that all patients were taking anticoagulant drugs at the time, they think it might have worsened the bleeding.

4. DONANEMAB

Sims *et al.* (2023) have reported the results of TRAILBLAZER-ALZ 2, a randomized, double-masked, placebo-controlled phase 3 trial of the Aβ-targeting monoclonal antibody donanemab in patients with early AD, funded by Eli Lilly and Company. Donanemab is an Ig G1 monoclonal antibody directed against the insoluble, modified, N-terminal truncated form of amyloid-β (Aβ) present only in brain amyloid plaques. Donanemab binds to the N-terminal truncated form of β-amyloid and aids plaque removal through microglial-mediated phagocytosis. The results from the trial have

been submitted by the sponsor for full approval of donanemab to treat patients with early AD to the FDA; the sponsor expects a decision by December.

The study design was a multicentre (277 medical research centres/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic AD (MCI/mild dementia (MD)) with amyloid and low/medium or high tau pathology based on PET imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023). Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met. The primary outcome was a change in integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0–144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the CDR-SB score (range, 0–18; higher scores indicate greater impairment). The authors have reported the following results:

"Among 1736 randomized participants (mean age, 73.0 years; 996 [57.4%] women; 1182 [68.1%] with low/medium tau pathology and 552 [31.8%] with high tau pathology), 1320 (76%) completed the trial. Of the 24 gated outcomes, 23 were statistically significant. The least-squares mean (LSM) change in iADRS score at 76 weeks was −6.02 (95%CI, −7.01 to −5.03) in the donanemab group and −9.27 (95%CI, −10.23 to −8.31) in the placebo group (difference, 3.25 [95%CI, 1.88-4.62]; P < .001) in the low/medium tau population and −10.2 (95%CI, −11.22 to −9.16) with donanemab and −13.1 (95%CI, −14.10 to −12.13) with placebo (difference, 2.92 [95%CI, 1.51-4.33]; P < .001) in the combined population. LSM change in CDR-SB score at 76 weeks was 1.20 (95%CI, 1.00-1.41) with donanemab and 1.88 (95%CI, 1.68-2.08) with placebo (difference, −0.67 [95%CI, −0.95 to −0.40]; P < .001) in the low/medium tau population and 1.72 (95%CI, 1.53-1.91) with donanemab and 2.42 (95%CI, 2.24-2.60) with placebo (difference, −0.7 [95%CI, −0.95 to −0.45]; P < .001) in the combined population. Amyloid-related imaging abnormalities of edema or effusion occurred in 205 participants (24.0%; 52 symptomatic) in the donanemab group and 18 (2.1%; 0 symptomatic during study) in the placebo group and infusion-related reactions occurred in 74 participants (8.7%) with donanemab and 4 (0.5%) with placebo. Three deaths in the donanemab group and 1 in the placebo group were considered treatment related."

Based on the above results, the authors concluded that donanemab significantly slowed clinical progression at 76 weeks in those participants with early symptomatic AD and amyloid and tau pathology with low/medium tau and in the combined low/medium and high tau pathology population. Donanemab treatment was associated with a lower risk of progressing from MCI (fully independent in daily activities) to MD (requiring assistance with some daily activities), or from mild to moderate dementia (requiring some assistance with basic self-care). In the low/medium tau group, donanemab slowed decline, demonstrated via scores on the iADRS and CDR-SB by 4.36 and 7.53months, respectively, over approximately 18 months in the trial. Notably, the incidence of death was 1.9% in the donanemab group and 1.1% in the placebo group, while the incidence of serious adverse events was 17.4% in the donanemab group and 15.8% in the placebo group. In the donanemab group, three participants with serious ARIA subsequently died. Treatment-emergent adverse events were reported by 759 of 853 participants (89.0%) receiving donanemab and 718 of 874 participants (82.2%) receiving placebo. Treatment discontinuation due to adverse events was reported in 112 participants receiving donanemab and 38 participants receiving placebo. The most common adverse events that led to treatment discontinuation were infusion-related reactions, either ARIA with oedema/effusion or microhaemorrhages and hemosiderin deposits, and hypersensitivity. As a major limitation of the trial, Rabinovic and La Joie (2023) pointed out the lack of racial and ethnic diversity, since only 2 American Indian/Alaska Native individuals, 11 Asian participants, 24 Black or African American individuals, and 71 Hispanic participants were included of 1251 US participants. Therefore, ethical concerns and the generalizability of results to populations at high risk for AD and dementia still continue to be issues that might spoil AD clinical trials.

5. CONCLUSION

In view of the above considerations, it seems that the use of monoclonal antibodies for AD treatment may be a new era for the pharmacological approach in the disease. Or at least it might indicate a new open door in the search to better understand the pathophysiology mechanisms involved in the illness. However, one should consider that the three drugs cited in this article are only approved, or at least submitted for approval, by the FDA; other health offices such as the European Medicines Agency (EMA) have not approved any of them yet (Morgan, 2023).

Outstandingly, a recent article by Molchan and Fugh-Berman (2023) has added some other arguments to the discussion on the new AD drug discovery projects. Although they recognize that one cannot compare different trials for different studied drugs for the same disease, they have discussed on the basis of the new monoclonal antibodies for AD and acetylcholinesterase inhibitors, namely donepezil, the first class of drugs approved for treating AD. The similarities in outcome measures between donepezil and β-amyloid protein antibodies for AD have been previously noted and a statistically significant change on a test or scale does not mean that the change is clinically significant. For instance, the authors have pointed out that on the CDR-SB scale, a minimal clinically meaningful difference is generally thought to be between 1.0 and 2.5 points annually. In a federally funded study in which participants

were tested annually, the mean change in CDR-SB score considered to be clinically meaningful for those with early AD was 1.63 points per year (Andrews *et al.*, 2019). This difference is greater than the change found in any of the lecanemab or donepezil studies to date. Thus, the authors affirm that neither the lecanemab trial nor the donepezil trials found clinically significant beneficial effects of AD drugs. Besides, they also considered that concerns about the adverse effects in the trial should not be taken for granted since they might be as serious as a risk of death. Finally, they also pointed out concerns on the cost of treating AD with monoclonal antibodies. When administered at the recommended dose of 10mg/kg once every 2 weeks, the annual cost of lecanemab is about US$26,500 a year. Therefore, the question that arose from the ideas from Molchan and Fugh-Berman (2023) was whether newer AD drugs are significantly better than the older ones. Well, may time be a strong ally to help answering such a putative question.

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