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Advances in immunotherapy for Alzheimer's Disease 2020-2023 – a literature review
Postępy w immunoterapii Choroby Alzheimera w latach 2020-2023 – przegląd literatury

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ABSTRACT

Introduction: Alzheimer's disease is an increasing problem in aging European societies. Almost 9 million Europeans already suffer from this disease.
The aim of this article is to provide an objective overview of new immunotherapy and vaccination methods among published research results from 2020-2023.

Materials and methods: This paper is based on medical articles collected in the PubMed database from 2020-2023. The research was conducted by analyzing keywords such as: "Alzheimer Disease," "Immunotherapy"/"Vaccination" and "Treatment."

Results: Recent years have seen a large increase in research directed at AD immunotherapy. Among these, those on aducanumab, donanemab and lecanemab are particularly noteworthy. Lecanemab and aducanumab are already registered in the US, among others. More studies should be expected to try to solve the problems of qualifying patients into the appropriate groups or increasing the number of variables in ongoing trials. This will allow an even more reliable evaluation of the molecules under study and, consequently, further registrations of medicinal products.

Keywords: Alzheimer Disease, Immunotherapy, Vaccination, Treatment,

STRESZCZENIE

Wprowadzenie: Choroba Alzheimera jest coraz powszechniejszym problemem w starzejących się społeczeństwach Europy. Na tę chorobę cierpi już prawie 9 mln Europejczyków.
Celem niniejszego artykułu jest obiektywny przegląd nowych metod immunoterapii i szczepień wśród opublikowanych wyników badań w latach 2020-2023.

Materiał i metody: Niniejsza praca opiera się na artykułach medycznych zebranych w bazie danych PubMed w latach 2020-2023. Badania przeprowadzono poprzez analizę słów kluczowych takich jak: "Choroba Alzheimera", "Immunoterapia"/"Szeczepienia" i "Leczenie".

Wyniki: Ostatnie lata to duży wzrost badań nakierowanych na immunoterapię AD. Wśród nich na uwagę zasługują szczególnie te nad aducanumabem, donanemabem i lecanemabem. Lecanemab i aducanumab są już zarejestrowane m.in. na terenie USA. Należy oczekiwać kolejnych badań, które spróbują rozwiązać problemy kwalifikacji Pacjentów do odpowiednich grup czy zwiększania ilości zmiennych w prowadzonych badaniach. Pozwoli to

na jeszcze rzetelniejszą ocenę badanych molekuł i co się z tym wiąże, kolejne rejestracje produktów leczniczych.

Słowa klucze: Choroba Alzheimera, Immunoterapia, Szczepienia, Leczenie

Pathogenesis of Alzheimer's disease

Alzheimer's disease (AD) belongs to the group of incurable neurodegenerative diseases. It leads to neurological damage associated with memory impairment and is the most common cause of dementia [1, 2].

Up to 95% of ADs are sporadic cases with no familial link. However, the risk of the disease has been shown to increase with age and with the presence of diseases such as diabetes (type 2), hypertension, heart failure, and depression (over 65 years). Low physical activity and limited social contact are also risk factors for AD [3, 4]. The pathogenesis of the disease is multifactorial, involving both genetic and environmental influences. Unfortunately, to date, it has not been established exactly which of these two groups of factors are decisive and to what extent they promote the development of AD [2]. However, a team of researchers has singled out a dozen genes that have a guiding role in this regard. Chief among them is the gene encoding the CD33 molecule, damage to which leads to dysfunction of the brain's immune system.

Despite this, the exact pathogenesis of the disease remains undetermined to date [5, 6]. The fact is the large role of beta-amyloid accumulation as the main pathological lesion. Under normal conditions, its excess is removed by the lymphatic system with the help of microglia. In a situation of dysfunction of this system, with damage to the gene encoding the aforementioned CD33, beta amyloid accumulates in the cells of the nervous system [5, 7, 8]. Beta amyloid (BA) itself is part of a larger protein that builds the nerve cell membrane. The presence of beta amyloid aggregates leads to reduced conduction at synapses connecting nerve cells and the development of chronic inflammation and activation of the immune system, which, instead of removing the plaques, perpetuates the chronic inflammation caused by their presence [1, 2, 4, 5, 8]. Granzotto A. and his team discovered that a problem in microglia

function signaling associated with AD is the loss of function of the TREM2 receptor. It is responsible for binding ligands, including beta amyloid. Granzotto believes that cells with lost function of this receptor may fail to bind beta amyloid and lead to amyloid accumulation, but this concept requires further research [6]. The two concepts above, both the role of the gene encoding the CD33 molecule and the role of the gene responsible for the TREM2 receptor in microglia, do not contradict each other, and further research on this topic is expected.

Traditional treatment methods

Treatment of AD is chronic and persistent, and primarily symptomatic. This is related to the long-held cholinergic hypothesis. For many years, it was recognised that an important element in the pathogenesis of AD was a decrease in acetylcholine (ACh) concentration at nerve cell synapses [9, 10]. Therefore, acetylcholinesterase inhibitors (IAChEs) were introduced for treatment to increase its concentration in synaptic gaps and limit the progression of AD. Unfortunately, studies have found that the efficacy of the above drugs is limited. They do not lead to reversal of lesions or slowing of disease progression. Despite this, IAChEs are still the largest group of drugs used in AD [9, 11]. This is explained by their antagonism to AD - in the disease, the number of nerve cells decreases, limiting the production of ACh, whereas IAChEs allow for the most efficient use of existing ACh. The aforementioned mechanism is weakened over time - fewer and fewer nerve cells produce less and less ACh, so IAChEs do not have the ability to limit disease progression. Donepezil, galantamine and rivastigmine, which are IAChEs, are used in AD therapy [12]. Clinical trials have shown their positive effect in phase I and II of AD. As for their efficacy in phase III (advanced) AD, there is debate. Howard et al. showed in their study that patients in advanced AD continued to benefit from Donepezil in terms of improving cognitive function and slowing the progression of dementia. Memantine, an NMDA receptor antagonist, is also used in therapeutics. It is designed to reduce the amount of L-glutamic acid present in the synapse. It is formed in damaged nerve cells and its excess leads to excitotoxicity - excessive activation of AMPA and NMDA receptors. By influencing this process, Memantine reduces the subsequent pathological changes caused by excess glutamate (e.g. neuronal damage or the further development of cognitive disorders) [12, 13].

Immunotherapy in Alzheimer's Disease

The key to finding a way to stop the development of AD seems to be a thorough understanding of the molecular pathways involved in its development. Such attempts were made many years ago. An example is Chinese folk medicine, where extracts of *Hupperzia serrata* were used. In the course of later research, analyses of the alkaloids contained therein began. The focus was on huperzine A, as a compound that may affect the correctness of WNT signalling, crucial for normal cell function [14]. The high level of interest in the development of AD pharmacotherapy is particularly evident in the scale of the number of studies being conducted. In 2012, there were slightly more than 1,000, while by the end of 2023, there are already 3317 clinical trials [15]. Immunotherapy is currently the most promising area of AD research. Among others, research is underway on monoclonal antibodies (mAbs) directed against beta-amyloid and the pathological tau protein [16, 17, 18].

In clinical trials, patients with early AD were included in the study group. It was found. that the use of anti-amyloid antibodies led to a reduction in amyloid plaque size. In 2022, the only immunotherapy approved was aducanumab, mAbs specific for amyloid beta, leading to a reduction in amyloid density. Variable antibody light and heavy chain fragments (scFVs) have shown potential in the treatment of AD [16]. PBD-CO6 is another mAbs under investigation, effective against a variant of beta amyloid containing pyroglutamate (pGlu) at the N-terminus, avoiding inflammation-related problems (complement inactivation and immunogenicity). It has the potential to remove beta amyloid aggregates, improving cognitive function in patients [17]. In 2020, lecanemab mAbs, which works by also targeting pGlu, were included in phase III trials. It has an effect on the BA variant containing pyroglutamate (pGlu) at the N-terminus, improving clinical signs of inflammation (complement inactivation and immunogenicity). It has the potential to remove beta amyloid aggregates, improving cognitive function in patients [18]. In recent years, there have been more than a dozen phase III clinical trials with mAbs: bapineuzumab [19, 20], solanezumab [21, 22], gantenerumab [23, 24, 25] and crenezumab [26, 27, 28], but none of them showed efficacy as assessed by cognitive improvement among the AD group. For this reason, I discuss three monoclonal antibodies in more detail in the following section – aducanumab, donanemab and lecanemab.

Review of current research on immunotherapy in AD

Aducanumab

Aducanumab is a mAbs directed against residues 3-7 on the N-terminus of BA [29]. The mechanism of BA removal involves microglia binding to the Fc region of the antibody, increasing the phagocytosis activity of the aducanumab-BA complex [30, 31]. Aducanumab reduces oligomeric neurotoxicity by blocking the binding of soluble BA complexes to metabotropic receptors and slowing their release into the neuropil from aggregates [31]. It also reduces calcium-induced neurotoxicity [29, 30, 32].

Preclinical studies showed that aducanumab administered intraperitoneally bound to diffuse and compact BA plaques in the brain of transgenic mice tested. Aducanumab did not affect BA concentrations in plasma or brain, confirming that it does not bind to soluble BA monomers. Aducanumab reduced the size of all forms of Aβ deposits by up to 70%, including a dose-dependent reduction in cortical and hippocampal activity [29, 32, 33].

The pertinent phase I study was the PRIME (n=165) trial, which was a phase 1b study involving participants enrolled on the basis of a positive amyloid beta PET scan and randomised to placebo or monthly intravenous aducanumab at 1, 3, 6 or 10 mg/kg body weight for 1 year. Aducanumab at doses of 3, 6 and 10 mg/kg body weight (b.w.) resulted in a reduction of BA plaques in the brain, as seen in a PET scan performed after 1 year [33, 34]. At 1 year, aducanumab induced a significant dose-dependent slowing of clinical progression as measured by the Clinical Dementia Rating Scale, with the greatest slowing observed at the 10 mg/kg b.w. dose [33, 34, 35].

Subsequently, aducanumab was investigated in the EMERGE(n=1638) and ENGAGE (n=1647) trials, two equally multicentre, randomised, double-blind, placebo-controlled phase3 studies on MCI and mild dementia. Participants were recruited on the basis of a positive amyloid beta PET scan and were randomly allocated (1:1:1) to a group receiving intravenous aducanumab at a dose of 6 mg/kg, 10 mg/kg or placebo, every 4 to 76 weeks. For the first time in the study, the APOE genotype was used in dose escalation regimens, due to the risk of ARIA (abnormalities on imaging studies due to AD). Participants received two dosing regimens - lower doses than the target for the first 3-6 infusions if they had APOE ε4 expression. The study also looked at the possibility of ARIA during the study. Continuation, temporary suspension or

permanent discontinuation occurred due to the type, magnitude and progression of ARIA [32, 33].

In the EMERGE study, the primary clinical outcome was achieved. At week 76, aducanumab administered at 10 mg/kg resulted in a 22% reduction in clinical progression. Aducanumab at 10 mg/kg i.p. also resulted in a smaller reduction compared to placebo in secondary endpoints, including a 27% reduction in cognitive decline.

There was a dose response tomAbs in both the EMERGE and ENGAGE trials.The mean reduction in brain BA levels compared to baseline was 71% in EMERGE and 59% in ENGAGE, while the achieved change in the placebo group was an increase of 4% and 1% in each trial, respectively. At week 78, 48% of patients in EMERGE and 31% of patients in ENGAGE received aducanumab therapy at 10 mg/kg.

Furthermore, in both EMERGE and ENGAGE, administered mAbs at a dose of 10 mg/kg b.w. reduced plasma tau protein levels by 13% and 16%, respectively. In contrast, the placebo groups showed an increase in plasma tau protein levels by 8% and 9%, respectively.Based on the combined data from EMERGE and ENGAGE, ARIA, both with oedema (ARIA-E) and/or haemorrhage (ARIA-H), combined were common (41.3% with aducanumab at 10 mg/kg b.w.), but the incidence of symptomatic ARIA was low, involving only about 20% of radiological cases, with clinical symptoms such as headache [32, 33, 34].

Differences in clinical results between EMERGE and ENGAGE led to the suspension of further studies. In addition, up to two-thirds of the participants in the study groups were altered during the study (in terms of dose), so the results had less validity. Despite this, Aducanumab was approved by the FDA as a treatment for mild dementia and mild cognitive impairment in 2021. This cited results showing a reduction in BA aggregates. The formulation is recommended for patients presenting similar symptoms to those included in the EMERGE and ENGAGE studies. The further fate of the formulation is dependent on verification of the benefits during further studies. [34]. Within the next few years, studies are due to start: EMBARK (phase 3 - evaluating the efficacy of this mAbs in subjects from previous studies) and ADUHELM ICARE AD-US (phase 4 - planned to confirm previously obtained results and to investigate the outcomes of long-term therapy) [34, 35].

Donanemab

Donanemab is an IgG1-class mAbs that targets the N-terminal truncated form of BA (BAp3-42) found in stable platelets. This form is toxic, subject to increased aggregation. The mAbs act by affecting BA so that its soluble form is unable to block recognition of its aggregates. This is mediated by microglia. In mouse studies, significant effects were achieved. Unlike classical antibodies, which reduced the number of BA plaques only when administered ma the beginning of life (about 9 months), donanemab worked even in older mice (over 23 months) [36, 37, 38].

Its efficacy was tested in the TRAILBLAZER-ALZ randomized trial. This was a double-blind, placebo-controlled study in subjects with mild cognitive impairment and dementia due to AD. Patients were qualified based on their PET results (BA and tau protein counts were assessed). Subjects with too low and too high their values were not included in the study. mAbs were administered at doses of 700 mg/kg per month, for 3 months, and then increased to 1400 mg/kg per month for up to 1.5 years. During Patients were modified in dosage according to changes in imaging findings. The primary endpoint of this multicenter study was a decrease in score, relative to baseline, on the iADRS (integrated Alzheimer's disease rating scale). Donanemab led to a slowing of the development of cognitive impairment, reduced BA levels and the amount of tau protein, as demonstrated by imaging studies. ARIA was observed in about 40% of the study population [37, 38].

Subsequently, the TRAILBLAZER-ALZ2 study was initiated, and is scheduled to be completed in 2025. It is expected to last more than 1.5 years and is a randomized, double-blinded phase 3 study. The inclusion criteria were the same as in the previous study. A recent announcement declares that a significant decrease in AD progression on the iADRS scale (by 35%) has been achieved [39].

The TRAILBLAZER-ALZ3 trial has also been initiated (scheduled completion 2027), which is a phase 3 study to evaluate the effect of donanemab in pre-symptomatic AD. The endpoint is expected to be time to symptom onset [40].

There was also a TRAILBLAZER-ALZ4 study (a phase 3 trial) to compare donanemab and aducanumab (inclusion criteria analogous to previous studies). The result is the number of subjects who achieved BA clearance in the brain within 6 months. This was achieved in just under 38% of the donanemab-treated population and just under 2% of subjects who received aducanumab. Donanemab also had a more favorable effect on reducing tau protein levels (p-tau217) over the six-month treatment period compared to baseline values [40].

Donanemab is currently in the TRAILBLAZER-ALZ5 (undergoing registration of mAbs in China for the indication of early AD) and TRAILBLAZER-ALZ6 (conducted to further understand ARIA using modern bio markers and MRI sequences for analysis) trials [40, 41].

Lecanemab

Lecanemab (BAN2401) is a mAbs showing affinity for soluble BA polymers. The Phase I study was completed in 2013. The study group consisted of patients with mild-to-moderate dementia who were administered escalating doses of lecanemab (0.1-10mg/kg b.w. every 2 weeks for 16 weeks). It showed good tolerability of the drug and a low incidence of ARIA [42]. Subsequently, a phase 2 study was conducted to determine the target dose of this mAbs, and the main clinical point of this study was the change in ADCOMS (AD composite rating scale) over the course of 18 months. During the course, it was determined that patients carrying APOE ε4 were not included in the study, due to the increased prevalence of ARIA in this population. The study resulted in a relationship indicating a dose-dependent effect achieved. The highest decrease in BA aggregates was observed in patients who used 10 mg/kg every 2 weeks for 1.5 years, as assessed by the ADCOMS scale [43, 44].

In 2019, NCT03887455, a Phase 3 study, was initiated, with similar inclusion criteria as in previous studies. The endpoint was change on the Clinical Dementia Rating Scale (CDR-SOB) after 1.5 years. Lecanemab produced a knowledgeable effect compared to placebo, further reducing the number of BA aggregates. Based on the results, the FDA approved Lecanemab for the treatment of MCI or mild AD-induced dementia in early 2023. This antibody, similar to aducanumab, was subject to an accelerated registration procedure [45, 46, 47].

AHEAD 3-4/5 is a randomized phase 3 study that is expected to last until 2027. The study includes subjects with moderate to advanced BA aggregates, as determined by PET. The study includes two groups - those treated with these mAbs (at a dose of 10mg/kg b.w. every month for 48 months) and placebo. The effect on reducing the amount of BA aggregates in the brain is being studied [44, 48, 49].

Vaccination against AD

We are currently in the process of evaluating a number of potential targets for AD vaccination. Despite reporting 140 vaccination procedures against beta amyloid deposition and 25 against tau protein deposition, none of the immunization procedures have been recognized by the FDA [50, 51]. The DNA vaccine AV-1959D, targeting the N-terminus of the beta amyloid epitope, has shown immunogenicity in animal studies, including primates, unfortunately with the exception of humans. Mice treated long-term with AV-1959D showed an increase in anti-β amyloid antibodies [50]. In humans, the aforementioned immunotherapy is not effective if given too late, after the development of clinical symptoms. In order to reduce the formation of beta amyloid aggregates, research has also been conducted on strategies to develop plant-derived vaccines. The first such immunization preparation was developed as early as 2002, but unfortunately, further studies were halted due to the presence of serious side effects - in the study group, as many as 6% of subjects developed meningoencephalitis (meningitis) during treatment. A precise link between the preparation and meningitis was not found. The influence of the development of an autoimmune response, triggered by the interaction of T lymphocytes, was postulated. Other studies have tested the concept of combining influenza virus vaccines with immunomodulators. It is postulated that blockade of the PD-1 checkpoint - affecting the inhibition of T-lymphocyte apoptosis (is an element in the pathogenesis of AD), in combination with immunization against influenza, provides a significant immunostimulatory effect [50, 52, 53]. Such treatment has provided a clinical benefit in reducing cognitive deficits and reducing the accumulation of amyloid beta aggregates in the mouse population, presumably by recruiting macrophages to the CNS. More recently, a vaccine (named Y-5A15) developed on yeast cells was also shown to have the effect of reducing BA plaque formation and limiting neuronal damage in animal models. For this purpose, the yeast cell wall was modified to contain elements found in the BA structure [53]. A phase I study of the Protollin vaccine was reported in late 2021. It is a combination of proteins derived from the outer membrane of N. meningitidis and the lipopolysaccharide of S. flexneri. This combination activates TLR2 and TLR4 receptors present in the nasal cavity. The cascade of immune responses leads to stimulation of lymph nodes present in the neck region, from where activated Th CD4+ lymphocytes target the CNS, ultimately affecting BA clearance in AD mice [54].

In 2023, the results of a Phase II study on the impact of the UB311 immunotherapeutic vaccine directed against BA were published. In the Phase I study, it was found to induce a sustained antibody response. The Phase II study, on the other hand, tested the immunogenicity and efficacy of the product and people with mild AD. The study lasted 78 weeks. The subjects

were divided into 3 equal groups - those receiving UB311 alone, UB311 and placebo, and placebo alone. The endpoints were safety of the formulation, tolerability and immunogenicity. At the end of the study, antibodies were recorded at 93%. Further studies are required for this formulation [55].

Summary

In recent years, we have seen significant progress in the development of immunotherapies against AD. At this point, two of the mAbs described above have passed a number of clinical trials, subject to FDA registration in the US - "LEQEMBI" (Lecanemab - July 2023) and "ADUHELM" (Aducanumab - June 2021). "LEQEMBI" has also been registered in Japan (September 2023). At the time of finishing this publication, "LEQEMBI" was also approved in China (early January 2024). These formulations were introduced with an indication for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild dementia due to AD.

In contrast to this positive information, we receive a whole gro reporting on the results of studies that show no effect of the particles used. There are also thousands of current studies. Among them, we can expect a similar percentage of studies that achieve the desired effect. This is largely influenced by how the research is conducted - its preparation, assumptions and conduct.

A major problem remains the correct planning and inclusion of people in the study group. An issue that needs to be clarified is the designation of study and control groups. The current rules of inclusion in many studies, unfortunately, are not quite ideal - this results in the inclusion of groups of people whose health problems do not fully correspond to a given study. Among neurological conditions, there are many diseases that follow a similar course or have a similar etiology. A flagship example of this is tauopathies, which, in addition to AD, are found in frontotemporal degeneration or post-traumatic encephalopathy, among others. Inclusion, which is based on the presence of a pathological tau protein, is not sufficient, as the study results in the exclusion of patients who do not have a final diagnosis of AD. The increased number of people excluded at various stages of the study reduces the reliability of the results. Another issue is population issues. The studies conducted focus on the white race, people of other races are very rare, which limits the possibility of using the results obtained in a global perspective. This may be dictated to some extent by socioeconomic considerations - making it difficult for the

often poorer part of the population to access the research. There are reports suggesting that BA levels may differ among different populations, including Hispanics and African-Americans. In the studies published to date, people from these groups have rarely been included, and thus we have little knowledge of the potential effects that the use of certain therapies might have in the populations in question. This is counterbalanced by the aforementioned studies, including TRAILBLAZER-ALZ 3 and AHEAD 3-4/5, where several tens of percent of participants are from the aforementioned populations.

The reliability of the studies is also compromised by elements beyond the control of the investigators - changing the size of the dose used depending on the occurrence of side effects (ARIA, among others). This results in the need to modify the dosing regimen, which further reduces the quality of the results obtained. Groups within groups are formed, which increases the number of variables that are increasingly difficult to analyze and draw correct conclusions based on them.

In conclusion, significant achievements have been made in the field of AD immunotherapy in recent years. With this in mind, we should look forward to further studies that will take into account the issues mentioned and try to improve what we have.

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