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PRACA POGLĄDOWA / REVIEW PAPER

Jacek Tabarkiewicz [1,2]

Advances in active and passive immunotherapy for Alzheimer's disease – a short review

Postępy w aktywnej i pasywnej immunoterapii w chorobie Alzheimera – krótki przegląd piśmiennictwa

[1] Zakład Immunologii, Samodzielna Katedra Medycyny Molekularnej, Wydział Medyczny Uniwersytet Rzeszowski
[2] Przyrodniczo-Medyczne Centrum Badań Innowacyjnych, Wydział Medyczny, Uniwersytet Rzeszowski

STRESZCZENIE

Choroby neurodegeneracyjne m.in. choroba Alzheimera (AD) dotykają rocznie miliony nowych pacjentów na całym świecie. Fakt ten spowodował intensywny rozwój terapii modyfikujących przebieg choroby i mogących mieć zastosowanie w AD. Dane przedkliniczne wykazały zaangażowanie układu immunologicznego w patogenezie choroby Alzheimera. Komórki mikrogleju, komórki prezentujące antygen np. komórki dendrytyczne oraz produkty aktywacji dopełniacza odgrywają aktywną rolę w neurodegeneracji. Z drugiej strony niektóre elementy układu odpornościowego mogą być wykorzystane do eliminacji złogów amyloidowych i innych nieprawidłowości związanych z AD. W związku z tym, metody pasywnej i aktywnej immunoterapii są jednym z najszybciej rozwijających się sposobów terapii choroby Alzheimera. Podawanie przeciwciał lub indukcja odpowiedzi immunologicznej przeciwko β-amyloidowi, α-synukleinie lub białku tau są intensywnie badane. Jest to związane z odkryciem, że białka te mogą być celem dla przeciwciał w przypadku ich ekspresji na błonie komórkowej lub w przestrzeni pozakomórkowej. Także stosowanie innych metod immunoterapii pasywnej

ABSTRACT

Disease-modifying alternatives are intensively developed for the treatment of neurodegenerative disorders, a group of diseases that afflict millions of patients annually. The pre-clinical data shown involvement of immune system in the pathogenesis of Alzheimer's disease (AD). Microglia cells, antigen presenting cells like dendritic cells and products of complement activation take an active part in neurodegeneration. On the other hand, some components of immune system could be used for elimination of amyloid plaques and another structural abnormalities associated with AD. Because of that, passive and active immunotherapies are one of the most developed approaches in therapy of AD. Vaccination against amyloid-ß, α-synuclein, or tau has been extensively explored, especially as the discovery that these proteins may propagate cell-to-cell and be accessible to antibodies when embedded into the plasma membrane or in the extracellular space. Also other methods of passive (intravenous immunoglobulins) and active (DNA based vaccines) are associated with positive clinical outcome. The clinical development of efficient and safe immunotherapies

Adres do korespondencji / Mailing address: Jacek Tabarkiewicz, Przyrodniczo-Medyczne Centrum Badań Innowacyjnych, Wydział Medyczny, Uniwersytet Rzeszowski; ul. Warzywna 1a, 35-959 Rzeszów, POLSKA; tel.: +48 17 ; e-mail: jtabarkiewicz@ur.edu.pl

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(podawanie dożylnych immunoglobulin) i aktywnej (szczepionki na bazie DNA) jest związane z pozytywnymi efektami klinicznymi. Kolejne próby kliniczne prowadzą do rozwóju efektywnych i bezpiecznych metod immunoterapii choroby Alzheimera i innych chorób neurodegeneracyjnych.
Słowa kluczowe: choroba Alzheimera, immunoterapia aktywna, immunoterapia pasywna

for Alzheimer 's disease and other neurodegenerative disorders is a field in constant evolution.
Key words: Alzheimer's disease, active immunotherapy, passive immunotherapy

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Introduction

Dementia is a worldwide medical and socio-economic problem and one of the major contributors to morbidity and global non-communicable disease burden, thus requiring the need for significant health-care interventions. Alzheimer disease (AD) is the most common cause of dementia and may contribute to 60–70% of cases and there are about 8 million new cases per year [1]. The pathogenesis of Alzheimer's disease (AD) is very complex, given that it covers genetic, environmental as well as immunologic factors. Misfolded and aggregated proteins are recognised by receptors expressed on microglia and astroglia, and activate an innate immune response characterised by release of inflammatory mediators, which contribute to disease progression and severity [2]. Research suggests that increase of the risk for sporadic Alzheimer's could be associated with genes encoding factors regulating glial clearance of misfolded proteins and the inflammatory reaction. Systemic inflammation and obesity induced mild inflammation also are likely to interfere with immunological processes of the brain and further promote AD progression [2, 3]. The disturbances in brain and systemic immune response could lead to condition called neuroinflammation, which is involving humoral and cellular factors of immune system. K.I. Mosher and T. Wyss-Coray suggested in their article, that ageing of microglia cells and impairments in their function could eventually lead to neurodegeneration and, in some cases, progression to AD. They also described the six "hallmarks of microglial aging" (senescence, dystrophy, impaired movement, altered signaling, impaired phagocytosis, and impaired proteostasis), which may be studied in the context of aging and AD [4]. The knowledge about active role of immune system in pathogenesis of AD and the fact, that current treatments do little to modify the disease progression lead to preclinical and early clinical trials, considering active and passive immunotherapies as promising disease modifying strategies for combating AD.

Amyloid-β (Aβ) directed immunotherapies

Amyloid-β (Aβ) peptide is the major component of senile plaques in AD patients and because of that is considered to play a key role in the pathogenesis of AD thereby leading to Aβ as a target for active and passive immunotherapies. Active immunization results in production of anti-Aβ, while in passive immunotherapy exogenous antibodies are delivered to patient's organism. AD models proposed several antibody-mediated microglial FcR-dependent and FcR-independent mechanisms of the removal of Aβ from the brain: clearance of plaques by phagocytosis, antibody-mediated direct disassembly of plaques, prevention of Aβ aggregation and neutralization of oligomer toxicity, peripheral sink effect by clearance of circulating Aβ, intracerebral sequestration of Aβ in a monomeric state, hydrolysis of Aβ by IgM; and antibody independent, cell mediated plaque [5]. Phase II/III clinical trials with the use antibodies targeting different forms of Aβ are ongoing: BAN2401 (recognizing protofibrils, phase II), crenezumab (aggregated species, phase II), gantenerumab (fibrils, phase III), and solanezumab (Aβ mid-domain, phase III) [6]. Other programs using antibodies such as bapinezumab (N-terminus, phase II/III) and ponezumab (C-terminus, phase II) have been discontinued as they did not meet expected goals [6]. a humanised mouse anti-human Aβ IgG1 monoclonal antibody (GSK933776) is evaluated in phase I clinical trial [7, 8]. Among the Aβ targeting therapies, the passive approach with the use anti-Aβ b monoclonal antibodies is the most advanced. However, active immunization strategies, like ACI-24 and Lu AF20513 vaccines, were introduced into phase I/II clinical trials [6]. Unfortunately, the active immunotherapy is associated with relatively high risk of autoimmune responses e.g. during active immunization using AN-1792 (full-length Aβ1-42 6% of the patients suffered with meningoencephalitis associated with T-cell infiltration [9]. Immunotherapies directed against Aβ successfully clear or neutralise the amyloid peptide's toxic forms, on the other hand progression of the disease were not stopped. Results of phase III clinical trials could suggest, that targeting amyloid in AD may not be an appropriate treatment option in cases in which the plaques are already developed. These high-profile failures may indicate that amyloid-based therapies need to be used at an earlier stages of the disease process, prior to plaque formation. Immunisation with novel agent - CAD106 demonstrated a favourable safety profile and in November 2015 Phase 2/3 trial began and is set to run until 2023, with a 5-year treatment period. This study

aims to homozygous ApoE4 carriers between the ages of 60 and 75 who are cognitively normal and will measure ability to delay diagnosis to MCI or AD dementia.

Tau directed immunotherapies

Microtubule-associated protein, tau exists as a protein within cells to assist in stability of the cytoarchitecture, especially in neurons. It is considered to play a crucial role in normal neural functioning, but when become misfolded and aggregated is one of the major components of the amyloid plaques and neurofibrillary tangles characteristic for Alzheimer's disease. The active immunotherapy with the use of phosphorylated tau epitopes has shown promising results in animal models [12]. The main goal of vaccination with tau epitopes is to elicit an immune response directed against certain pathological conformers of phosphorylated tau without also mounting autoimmune reaction against physiological forms of this ubiquitous intracellular protein. Two phase I trials (AADvac-1 and ACI-35) were focused on the use of active immunisation with tau epitopes in the treatment of Alzheimer's disease [6]. The monoclonal antibodies against phospho-tau and tau oligomers have also been developed and in 2014-2015 3 of phase I clinical trials (RG7345, BMS-986168, C2N 8E12) were initiated. .

α-Synuclein directed immunotherapies

α-Synuclein (α-Syn) is a synaptic protein involved in synaptic transmission and vesicle release and was identified in AD brains associated with plaque formation and neurodegeneration [11]. Despite the fact, that α-Syn was initially associated with AD, all currently ongoing clinical trials based on active or passive immunotherapies targeting this protein are focused on Parkinson's disease [6].

Other approaches for active and passive immunotherapy of AD

Intravenous Immunoglobulin (IVIG) - the human polyclonal IgG antibody preparation has been under study as a potential treatment for AD since 2002. In clinical trials IVIG treatment resulted in measurable alterations in plasma amyloid levels, however it had not a major impact on the progression of disease [13]. In pre-clinical studies, the anti-prion protein (PrP) antibodies were shown to be able to reduce Aβ-related synaptotoxicity and these results provide an in vivo evidence of principle for such a therapeutic strategy [14]. The complement factor C5a and its receptor have been found to be up-regulated in microglia in the surroundings of amyloid plaques and this findings lead to idea, that blocking of C5aR could be beneficial in AD. In a mouse model of Alzheimer's disease, immunisation with C5a-peptide reduce microglia activation and thus neuroinflammation associated with reduced neuronal dysfunction and AD symptomatic decline [15]. Vaccines based on dendritic cells were tested for active immunotherapy of cancers in humans. Cheng J et al showed in animal based study, that dendritic cell-based therapy could be an effective treatment for AD [16]. Another new method for treatment of AD tested in murine Alzheimer's model indicated that increased cerebral infiltration of monocytes, either by enrichment of their levels in the circulation or by weekly immunization with glatiramer acetate, resulted in significant reduction of disease progression by mechanisms that involved enhanced cellular uptake and enzymatic degradation of toxic amyloid-β as well as regulation of brain inflammation.

Conclusions

Active and passive immunotherapies were proved to be very efficient in clearance or reduction of cerebral or plasma concentration of amyloid-β and another molecules associated with development of Alzheimer's disease. Unfortunately, the clinical studies did not lead to promising clinical results. Especially, the active immunisation with Aβ was associated with relatively high number of adverse effects. Amyloid-related imaging abnormalities (ARIA) ist the major severe side effect of Aβ directed immunotherapy. The frequency of ARIA could be reduced by monitoring of CSF anti-Aβ autoantibody, which could biomarker for ARIA in clinical trials [18]. New antibodies and vaccines are tested for their safety and efficacy in ongoing clinical trials. The active and passive immunotherapy seems to be promising treatment especially for patients in prodromal or early phase of Alzheimer's disease. Also, development of biomarkers, which could be used in monitoring of adverse effects of therapy is crucial for improvement of safety and increase of positive clinical outcomes in immunotherapy of AD.

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