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REVIEW PAPER

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Clinical application of monoclonal antibodies in targeted therapy

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ABSTRACT

Introduction. Recently, monoclonal antibodies (mAbs) have become powerful human therapeutics in the diagnosis and treatment of many diseases. Drugs based on mAbs are approved for the treatment of cardiovascular, respiratory, hematology, autoimmunology, and oncology diseases.

Aim. To present the current state of knowledge about the application of mAbs in the therapy of various diseases such as cancer, autoimmune and Alzheimer's diseases.

Material and methods. We conducted a thorough review of the scientific literature from the following databases: EBSCO, PubMed, Science Direct, and Springer Link.

Results. Currently, the Food and Drug Administration (FDA) has approved more than 50 therapeutic mAbs which are applied in various clinical trials. Action of mAb are based on various mechanisms, including directly targeting the cells, modifying the host response, recognizing and degrading molecules as well as delivering cytotoxic moieties.

Conclusion. Despite some limitations including side effects, and therapeutic challenges, monoclonal antibodies are an attractive option for the development of new therapies and molecular drug targets against a wide range of common diseases due to their specificity and flexibility. MAbs are considered as a great hope for medicine, and effective and safe drugs in the treatment of various diseases.

Keywords. cancer, inflammatory bowel diseases, Alzheimer's disease, immunotherapy, targeted therapy

Introduction

Monoclonal antibodies (mAbs) are specific antibodies that have the same specificity for an antigen and the same affinity for it. All antibodies are obtained from one B cell clone. Generally, monoclonal antibodies are IgG glycoproteins composed of two light and heavy polypeptide chains linked by a disulfide bridge. In each of the chain types there are variable antigen-binding fragments - Fab and Fc fragments, constant for all isotypes of the given isotype, the presence of which is associated with the activation of the immune system after the antibody binds with the antigen. The interaction of an antibody with an antigen most often inhibits the activity of the protein that it binds. Monoclonal antibodies are

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used in many fields of medicine: oncology, dermatology, transplantology, cardiology, hepatology, immunology, and laboratory diagnostics (Fig. 1).[1]

Monoclonal antibodies can be divided based into groups on their origin as chimeric, chimeric/humanized, humanized, or fully human. Their use in oncology is associated with their selective interaction with a well-defined molecular target in cancer cells that leads to blocking oncogenesis pathways. Monoclonal antibodies affect cancer cells by activating an immune response in an antibody-dependent cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[2] Cancer cell death may also occur as a result of the antibody's enhancement of apoptosis, modulation of the ligand-receptor reaction or blocking of a specific receptor for growth factor.[3] Targeted treatment is also directed at interfering with the angiogenesis within the tumor.[4] In order to increase the effectiveness of immunotherapy, antibodies can be combined with radioisotopes, toxins, cytostatics or cytokines that they would become antibody drug conjugates.[5] Currently, Food and Drug Administration (FDA) has approved more than 50 therapeutic mAbs which are applied in various clinical trials.

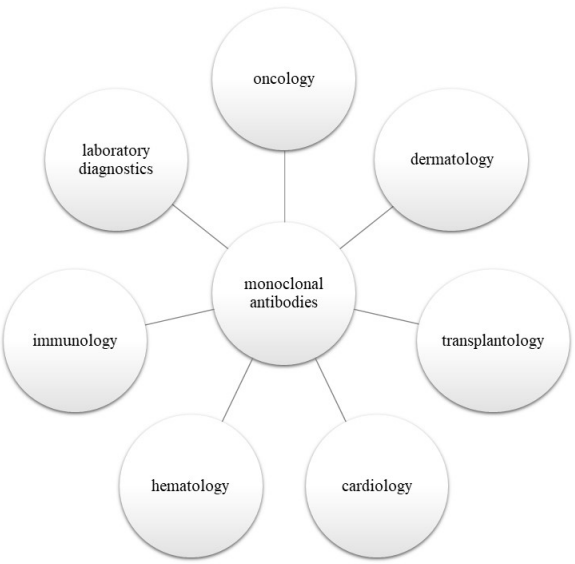

Fig. 1. Fields of application of monoclonal antibodies

Application of monoclonal antibodies in therapy

Cancer

For several years, a constant increase in the incidence of cancer has been observed around the world. High hopes for improvement of treatment results are associated with the implementation of therapy directed at specific molecular targets. One of the most promising therapeutic targets is the epidermal growth factor receptor (EGFR).[6] Blocking the EGFR by binding it to a specific antibody is therefore a validated method of targeted therapy in many cancers. Firstly, cetuximab (Erbitux™) is a chimeric, human-mouse monoclonal antibody of the IgG1 class, while panitumumab (Vectibix) is a completely human monoclonal antibody of the IgG2 class. MAbs against EGFR bind to the extracellular domain of EGFR in its inactive state. Mab against EGFR and EGFR compete for receptor binding by occluding the ligand-binding region, and thereby block activation of ligand-induced EGFR tyrosine kinase leading to subsequent degradation. The consequence of the action of cetuximab and panitumumab is the intensification of apoptosis by increasing expression of pro-apoptotic proteins, reduction of synthesis and secretion of proangiogenic factors, blocking in cancer cells repair of DNA damage caused by chemo-and radiotherapy, as well as inhibition of cell cycle progression.[6-9] Currently, evaluation of mutations in the KRAS proto-oncogene is considered essential for the selection for anti-EGFR therapy in colorectal cancer. In many published papers, it has been demonstrated that the mutation in the KRAS gene results in the abolition of the therapeutic effect of the drug aimed at inhibiting EGFR activity. The results of numerous retrospective and randomized phase II and III clinical trials suggest that the activating mutations in KRAS are recognized as a strong predictor of resistance to EGFR-targeted mAbs in colorectal cancer.[10-12]

On their basis, the assessment of the presence of mutations in the KRAS gene should be a standard element of the qualification of patients with advanced colorectal cancer for therapy with the use of cetuximab and panitumumab. Available data indicate that patients with the KRAS mutation should not be treated with anti-EGFR monoclonal antibodies because they not only do not benefit them, but their use may result in worse treatment results with simultaneous exposure to side effects such as skin toxicity and hypomagnesaemia.[13-15] Currently, cetuximab is also used for the treatment of patients with head and neck squamous cancer.[16] Another example of targeted therapy introduced for the treatment of patients with colorectal cancer is the use of bevacizumab (Avastin), a monoclonal antibody directed against the vascular endothelial growth factor (VEGF), which plays an important role in the process of angiogenesis. Bevacizumab is a recombinant humanized IgG1 monoclonal antibody produced by recombinant DNA. It binds VEGF selectively and neutralizes all its isoforms, which blocks the cell-induced VEGF-induced proliferation. This drug, binding the main factor responsible for neoangiogenesis, leads to inhibition of the formation of new vessels, regression of vessels already produced, and reduces the pressure inside the tumor, which causes that cytostatic drugs reach the cancerous tissues more effectively.[17] The use of bevacizumab does not increase the toxicity of chemotherapy and is well tolerated by patients.[18] In colorectal cancer, it is used in combination

with chemotherapy in the first wave of palliative disease. Bevacizumab is also currently being approved for the treatment of patients with non-small-cell lung cancer, ovarian cancer and glioblastoma.[19-21] Overexpression or amplification of the human epidermal growth factor receptor 2 gene (HER2) is found in 15-30% of cases of invasive breast cancer.[22] This feature is associated with a more aggressive course of the disease. Trastuzumab (Herceptin) selectively binds to the HER2/neu receptor present on the surface of cancer cells from breast cancer. Trastuzumab is a humanized monoclonal antibody directed against the HER2/neu receptor belonging to the EGF receptor family that by binding to the extracellular fragment of the receptor inhibits signaling to the cell nucleus while accelerating the internalization and degradation of the HER2 receptor.[23] This mAb is a potent activator of antibody-dependent cellular cytotoxicity and complement system. Reports revealed that mAb increases the effectiveness of chemotherapy both in the treatment of disseminated cancer and in adjuvant treatment after surgery.[24] Trastuzumab is approved for the first-line treatment of patients with metastatic breast cancer in combination with chemotherapy, in the palliative treatment of postmenopausal patients, positive for hormone receptors in combination with an aromatase inhibitor, and in monotherapy in patients who received so far, at least two treatment regimens due to the spread of the disease, involving anthracyclines and taxanes.[24,25]

The results of the conducted research allow to conclude that the use of trastuzumab in adjuvant treatment in patients with overexpression of the HER2 receptor reduces the relative risk of relapse of the disease.[26] The use of trastuzumab in adjuvant therapy is effective in eradicating axillary lymph node metastases and HER2 receptor overexpression.[27] Treatment of patients with trastuzumab have some side effect such as alopecia, nausea, diarrhea, and cardiotoxicity.[26,28]

Non-Hodgkin's lymphomas constitute a group of cancers of the lymphatic system that is diverse in terms of clinical course, treatment and prognosis. Almost 85% of lymphomas originate from B lymphocytes. The CD20 surface antigen is present on over 90% of B cell lymphoma cells and chronic lymphocytic leukemia. It does not peel off the cell surface, modulate or internalize.[29] The chimeric human-mouse monoclonal antibody directed against the CD20 antigen, rituximab (Rituxan) is widely used in the treatment of non-Hodgkin's lymphomas. It is the first monoclonal antibody registered in 1997 by the FDA in oncology. It is currently used in the treatment of follicular lymphomas and in the treatment of large cell lymphomas expressing CD20, as well as in chronic lymphocytic leukemias. The antibody, by binding to CD20 antigen on the cell surface, triggers cell lysis mechanisms via ADCC and CDC.[30] Rituximab also induces cell apoptosis. The CD20 antigen acts as a calcium channel. The increase in calcium concentration in the cytoplasm initiates apoptosis.[31] This drug, causing the breakdown of lymphoma cells, increases the presentation of tumor antigens by activating specific T lymphocytes. In monotherapy, rituximab elicited a response in more than 50% of B-cell indolent lymphomas. In combination with chemotherapy, however, it induced an answer in 90-100% of cases.[32] In patients with high nodal mass, the use of immunotherapy can cause tumor lysis syndrome.[33] Radioimmunotherapy is a method of cancer treatment in which the monoclonal antibody selectively destroys cells on whose surface a specific antigen is found, e.g. CD20, whereas the radiation emitted by the antibody-bound isotope destroys neighboring cells, including cells that are difficult to access or with insufficient expression of antigen. Lymphoma cells belong to very radioactive cells.[34] In the treatment of non-Hodgkin's lymphomas, two mouse monoclonal antibodies connected with radioisotopes: ibritumomab and tositumomab are registered. Ibritumomab Tiuxetan (Zevalin) is an immunoconjugate of a mouse antibody that recognizes a CD20 antigen on the surface of tumor-transformed B-lymphocytes with tiuxetan, a selective Indu-111 and Itru-90 chelator.[35]

In contrast, 131I-tositumomab (Bexxar) is a mouse IgG2a class antibody directly bound to radioactive iodine (131I) emitting beta and gamma rays. 90Y-Ibritumomab emits beta radiation with higher energy and greater penetration distance in tissues than 131I-tositumomab, additionally has a more favorable half-life.[36]

Currently, only one immunotoxin, gemtuzumab ozogamicin (Mylotarg), is used in anti-cancer therapy as drug against acute myeloid leukemia. This mAb is a combination of recombinant, humanized IgG linked to a cytotoxic derivative of calicheamicin.[37] The constant regions contain human sequences, while the variable regions are derived from a murine antibody that recognizes the CD33 protein. The immunoconjugate has been registered for the treatment of acute myeloid leukemia in patients over 60 years who were insensitive to therapy with other chemotherapeutic agents.[38] In the treatment of leukemia, new mAb is introduced - epratuzumab (EMab) - a humanized antibody directed against CD22 on B lymphocytes, which is an immunoregulator affecting the activation of the B cell antigen receptor. After binding to CD22, epratuzumab's predominant antitumor activity appears to be mediated through ADCC. Epratuzumab is safe in the dosing scheme in more than 85% of children affected by acute lymphoblastic leukemia.[39] Epratuzumab is also used for the treatment of systemic lupus erythematosus.[40] Monoclonal antibodies which are used in oncology are presented in Table 1.

Autoimmune diseases

Rheumatoid arthritis (RA) is a frequently occurring autoimmune disease that causes progressive limita-

Table 1. Monoclonal antibodies currently FDA-approved in cancer therapy

Name	Trade name	Type of antibodies	Molecular target	Main therapeutic application
Panitumumab	Vectibix	human IgG2	EGFR	colorectal cancer
Cetuximab	Erbitux	chimeric IgG1	EGFR	colorectal cancer
Bevacizumab	Avastin	humanized IgG1	VEGF	colorectal cancer
Trastuzumab	Herceptin	humanized IgG1	HER2	breast cancer
Rituximab	Rituxan	chimeric IgG1	CD20	non-Hodgkin's lymphomas
Ibritumomab-tiuxetan	Zevalin	murine IgG1	CD20	non-Hodgkin's lymphomas
Tositumomab-I131	Bexxar	murine IgG2a	CD20	non-Hodgkin's lymphomas
Epratuzumab	EMab	humanized IgG1	CD22	acute myeloid leukemia
Gemtuzumab ozogamicin	Mylotarg	humanized IgG4	CD33	acute myeloid leukemia

tion of mobility, extra-articular organ damage, premature death and socio-economic problems. Among the available preparations used in the treatment of RA are drugs based on monoclonal antibodies. Certolizumab pegol and infliximab are directed against tumor necrosis factor α (TNF-α), which is involved in the development of inflammation during disease. TNF-α plays a central role in the pro-inflammatory cytokine cascade and stimulates the liver to produce acute phase proteins, stimulates phagocytosis and attracts neutrophils into the joints. Certolizumab pegol (Cimzia) is a PEGylated Fab' fragment of a recombinant humanized antibody, what increases the plasma half-life of mAb.[41] Infliximab (Remicade) is a chimeric immunoglobulin G1, monoclonal antibody which contains a human constant region and a mouse-derived murine variable region.[42] Golimumab is the latest, second-generation mAb approved by the FDA as anti-TNFα drug with efficacy and safety in treatment of RA. It belongs to human IgG1κ monoclonal antibody class produced by a murine hybridoma cell line with recombinant DNA method.[43]

Rituximab is also used in RA therapy. There are two theories to explain the role of anti CD20 drugs in therapy. The first assumes that elimination of B lymphocytes prevents their transformation into plasmocytes, producing autoantibodies, which results in a decrease in the secretion of TNF-α by macrophages. According to the second theory, the lack of B lymphocytes, which are antigen presenting cells, reduces the activity of T lymphocytes, which leads to the reduction of synovitis related to them. The use of rituximab in therapy is quite safe, however, it is problematic because the treatment with these drugs is long-lasting and might cause small risk of serious events such as infection and hypogammaglobulinemia.[44,45] Next, mavrilimumab (CAM-3001) is a high-affinity, immunoglobulin G4 monoclonal antibody (mAb) against the granulocyte macrophage colony-stimulating factor (GM-CSF) receptor-α chain. Clinical trials in RA patients treated with mAb have shown benefit outcomes with respect to both efficacy and safety with no serious side effects.[46]

In patients with RA, mAbs reduces the clinical signs and symptoms of active disease and inhibits the progression of structural joint damage. However their use may be associated with serious side effects such as serious infection or reactivation of chronic infections, such as Herpes Simplex Virus, hepatitis C and hepatitis B virus.[47]

Crohn's disease (CD) is a chronic disorder that affects the functioning of the digestive system, and thus the quality of life of the patient. The pathogenesis of this disease is unknown, but clinical and experimental evidence suggests that uncontrolled activation of T lymphocytes causing inflammation is the main cause. Therapy with drugs that inactivate pro-inflammatory factors, i.e. TNF-α, in many cases results in remission of the disease. Such medicines include Infliximab, a chimeric monoclonal antibody that is designed to inactivate TNF-α, and may also induce apoptosis of T lymphocytes in the intestinal mucosa.[48]

A relatively new generation of vedolizumab (Entyvio), a humanized monoclonal antibody, can be used in the absence of a response to TNF-α inactivators. It recognizes the α4β7 integrin - a glycoprotein found on the cell membrane of some T and B lymphocytes. A4β7 interacts with MAdCAM-1 - a molecule present in the intestinal vascular network responsible for lymphocyte adhesion. Vedolizumab blocks the migration of lymphocytes into the gastrointestinal tract, while not stopping the migration of white blood cells into the central nervous system.[49] Studies show that the therapy is effective, but may have side effects such as serious infections and adverse events such as nasopharyngitis, headache, joint pain, nausea, and fever leading to hospitalization.[50]

Adalimumab (Humira®) is next mAb which found application in treatment of inflammatory bowel diseases and has positive impact on endoscopic mucosal healing.[51] It is an IgG1 monoclonal antibody that targets TNF-α which was approved by FDA in 2002 to is used in treatment of moderate to severe cases of CD for symptom control and inducing and maintaining clinical remission.[52]

Multiple sclerosis (MS) is a chronic inflammatory-degenerative disease of the central nervous system, characterized by multifocal inflammatory changes and the accompanying demyelination, which leads to axonal damage and loss. The pathogenesis of MS is unclear. In the treatment of MS, drugs based on mAbs are also used. Alemtuzumab (CAMPATH) is a humanized monoclonal antibody directed against the CD52 differentiation molecule, which is approved from 2013 for treatment of relapsing multiple sclerosis.[53] The mechanism of mAb application in MS involves immunomodulation by the depletion and repopulation of lymphocytes. After binding of alemtuzumab to lymphocytes, mAb results in the rapid, but long-lasting depletion of circulating CD52-positive cells, and the mechanism of lymphocyte depletion includes ADCC, CDC and apoptosis induction.[54] Natalizumab (Tysabri) is the only mAb currently approved from 2004 for relapsing-remitting form of MS. It acts by targeting lymphocyte migration across the blood-brain barrier, an early stage in MS lesion development. Report shows that about 6% of patients treated with natalizumab developed persistent antibodies which result in reduced efficacy.[55] Rituximab has also been used in a phase II trial in primary progressive form of MS. Ocrelizumab (Ocrevus®) is a next humanized anti-CD20 monoclonal antibody approved for the treatment of adults with relapsing or primary progressive MS. Simultaneously, mAb is considered as valuable new treatment option for delaying progression in early MS and first approved antibody for secondary progressive form of MS.[56]

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to the death of the patient. It is characterized by cognitive impairment, loss of long-term memory, language difficulties and aggression. The exact cause of AD is unknown, but two major theories that explain the molecular basis of AD are now widespread. One of them explains that AD is caused by the accumulation of toxic fibrillar β-amyloid deposits (Aβ), which is a toxic form of the protein responsible for impaired calcium cell metabolism and the induction of its apoptosis. The second hypothesis explaining the cause of AD is that pathological forms of tau protein initiate a cascade of disease. Hyperphosphorylated tau protein fragments combine to form neurofibrillary tangles inside the pericarion of nerve cells. It is possible that both Aβ deposits and pathological forms of tau protein affect cognitive functions and memory, causing AD.[57]

However, current studies on passive immunization of AD patients using mAbs allow to think about the actual inhibition of the progression of neuropathological changes in AD.

MAbs that can potentially be used in the treatment of AD are divided into two classes: human (e.g., gantenerumab, aducanumab) and humanized (e.g., bapineuzumab, solanezumab, crenezumab). Monoclonal antibodies used in the treatment of AD are shown in table 2. MAbs are designed to be associated with specific Aβ epitopes, contributing to its degradation. The mechanism of action of mAbs is not fully understood, however it is assumed that after the mAb crosses the blood-brain barrier, it connects to specific Aβ epitopes and then the effector Fc fragment.

After that the complement system and microglia cells are activated, which phagocytose Aβ, reducing its amount in the brain. However, it is uncertain whether it will be necessary to get mAbs into the brain at all, because the other proposed mechanism of action of mAbs is the peripheral sink hypothesis, according to which the antibody does not go to the brain but binds to free Aβ in the peripheral blood, lowering its concentration. This changes the balance of Aβ across the blood-brain barrier, with the result that Aβ flows away from the brain into the peripheral blood, striving to equalize Aβ concentrations on both sides of the blood-brain barrier.[58]

Hypothetically, there is a decrease in Aβ concentration in the brain and inhibition of neuropathological changes caused by its accumulation. However, although in clinical trials monoclonal antibodies such as ponezumab and solanezumab have been shown to act by this mechanism and a reduction in serum Aβ40, no significant clinical effects have been observed with ponezumab and solanezumab treatment.[59]

In general, the safety and tolerability profile of mAbs is acceptable. The only side effect observed, which should be given special attention, is amyloid-related imaging abnormalities (ARIA). There are two types of ARIA - ARIA-H and ARIA-E. ARIA-E refers to brain edema that is noticeable in an MRI scan caused by the breakdown of tight endothelial connections in the brain blood barrier and, as a consequence, accumulation of cerebrospinal fluid at this site. ARIA-H is characterized by excessive accumulation of iron contained in proteins (hemosiderosis), which is considered to be the cause of microhemorrhage, which is also representative of ARIA-H.

The etiology of ARIA remains unclear, although vascular Aβ is thought to be a factor that increases the permeability of blood vessels, which causes symptoms indicative of ARIA. In search of the relationship between ARIA and the use of mAbs, it was observed that with increasing the dose of bapineuzumab, the incidence of ARIA-E increased. It was also found that not all mAbs may contribute to the emergence of ARIA. Probably this effect is caused only by mAbs binding to the N-terminal section of fibrillar Aβ - bapineuzumab, gantenerumab and aducanumab. In clinical trials, mAbs such as crenezumab or BAN 2401 ARIA were not observed at all, and in case of solanezumab, only 1% of subjects (11 patients

Table 2. Monoclonal antibodies tested in AD therapy

Monoclonal antibodies	Type of antibodies	Mechanism of action	Results of clinical trial
Bapineuzumab (AAB-001)	huminized IgG1	Recognizes the N-terminal part of Aβ, leads to the degradation of excess fibrillar, soluble form of β-amyloid. It binds to the. MAb stimulates phagocytic microglia and cytokine production.	Clinical trials were unsuccessful due to the lack of proven clinical benefits and serious adverse effects in AD patients.[63]
Solanezumab (LY2062430)	humanized IgG1	Recognizes monomeric and soluble Aβ and leads to its sequestration and shifts the balance between the various forms of Aβ. MAb removes small, soluble forms of Aβ, which are directly toxic to the functioning of the synapses.	Clinical trials were unsuccessful - no improvement in cognitive or memory status in AD patients was noted. In patients with a mild form of AD inhibition of disease progression was observed.[64]
Gantenerumab (RO4909832, 1G1450)	human IgG1	Recognize the N-terminal and central part of monomeric, oligomeric, and fibril Aβ. Degrades amyloid deposits by recruiting microglia and activating phagocytosis.	Clinical trials have shown a reduction in amyloid deposits in PET. Phase III studies are currently underway.[64]
Crenezumab (MABT5102A, RG7412)	humanized IgG4	Recognizes monomers and aggregated forms of Aβ with a 10-fold–higher affinity for oligomers. MAb removes excess Aβ by stimulating its phagocytosis. It inhibits the release of pro-inflammatory cytokines, counteracting cerebral edema.	Crenezumab has been declared safe for humans. In the second phase of clinical trials, PET scans showed a reduction in β-amyloid accumulation, however, mAb did not cause improve cognition.[65]
Ponezumab (PF-04360365)	humanized IgG2δA	Recognizes C-terminal part of monomeric forms of Aβ. It reduces the deposition of Aβ in the cerebral blood vessels, improving their functioning.	MAb was generally safe and well tolerated. In mild-to-moderate AD subjects, no changes in Aβ were found. There was also no improvement in brain amyloid burden and cognition.[66]
Aducanumab (BIIB037)	human IgG1	Recognizes conformational epitopes of aggregated β-amyloid forms.	A dose-dependent clinical response and a reduction in brain Aβ plaques were observed in PET.[67]
BAN2401 (mAb158)	humanized IgG1	Recognizes soluble Aβ protofibrils. MAb protects neurons, reducing the toxicity of Aβ in the brain and cerebrospinal fluid.	Clinical trials confirmed the safety and good tolerance of mAb15 by the human body.[68]
BIIB092 (BMS-986168, IPN007)	humanized IgG4	Recognizes the N-terminal domain of tau and neutralizes its toxicity. Reduction in the amount of free tau in the cerebrospinal fluid was noted.	BIIB092 is safe and well tolerated.[69]
C2N-8E12 (ABBV-8E12)	humanized IgG4	Recognizes aggregated, extracellular form of pathological tau. Reduction in brain tau, microglial activation, and tau--seeding activity detected in brain lysates. improving also cognitive deficits.	Preclinical studies have demonstrated the improvement of cognitive deficits. Phase I trials confirmed the medicine's safety.[70]

treated with solanezumab and 5 who received placebo) confirm that this result is not statistically significant. The positive feature of ARIA is that it is easy to control, because stopping the administration of mAbs results in the resolution of side effects.[58-62]

Current clinical trials for the treatment of AD using mAbs, despite promising theoretical foundations, have produced quite disappointing results. Tests on bapineuzumab and solanezumab - so far, the largest projects taking part in the third phase of clinical trials did not give clinically positive results. This could be due to low doses administered to patients, too advanced disease or poorly designed mAbs, targeting the wrong kind of Aβ.

This indicates the limitations associated with the use of mAbs. However, in the absence of effective AD therapy, screening for passive immunization should continue. Currently, many new mAbs targeting different Aβ epitopes are tested and clinical studies are performed.

Conclusion

Due to the huge number of current research, the potential therapeutic use of monoclonal antibodies is rapidly increasing, but it is still relatively rare and still largely belongs to unconventional methods of treatment. Nevertheless it is a rapidly growing branch of medicine with a huge and unused therapeutic potential should still be studied and developed because the use of mAbs in therapy in many cases turns out to be more effective and safer for the patient. Moreover, monoclonal antibodies may turn out to be a "miracle" drug for many incurable diseases such as many type of cancer including colorectal, breast cancer, lymphomas and leukemia, rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis as well as Alzheimer's disease.

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