Document heading doi: 10.21276/apjhs.2019.6.1.23 **Review Article**

How can immunotherapy be used to target Amyloid Beta for treating Alzheimer Disease?

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Received: 14-02-2019 / Revised: 22-03--2019 / Accepted: 26-03-2019

Abstract

Neurodegenerative diseases including Alzheimer's disease are characterized by the build-up amyloid beta plaques resulting in non-regenerative nerve cell death. The nerve cell death causes limited brain activity, that triggers damage to cognitive and memory. Currently, no therapy for Alzheimer's disease is available and patients are treated for alleviating the symptoms. One of the suitable options could be antibody immunotherapy.The aim of this review to discuss antibody immunotherapy for the removal of amyloid beta plaques. The monoclonal antibodies bind amyloid beta plaques. This interaction leads to the activation of microglia in the nerve tissue and cleaning of deposits. The process of cleaning of amyloid deposits halts the brain damage, declines death of nerve tissue to maintain synaptic integrity of the brain. Immunotherapy leads a promising approach as a treatment option for Alzheimer's disease because it targets the key mechanism by which nerve damage is being caused. However, with the limitation of monoclonal antibodies in order to cross the blood-brain barrier, the immunotherapy remains the key factor in making a viable treatment for patients with Alzheimer's disease. Although, there are methods been tested to increasethe absorption of monoclonal antibodies through the blood-brain barrier.

Keywords: Alzheimer's disease, beta-amyloid plaques, monoclonal antibody, transporters, Blood-brain barrier, Immunotherapy, Acetylcholine.

Introduction

Alzheimer Disease (AD) affects approximately 50 million people worldwide in 2017 becoming one of the most expensive diseases to take care of [1]. It is estimated to cost $605 billion and the rate of growth for this disease will continually grow by 68% until 2050 [1, 2]. This is largely due to the increased life expectancy with a fast-growing older population especially in China, India but also in economically developed countries like UK and USA, making chronic diseases like AD more prevalent [1, 3].The increased life expectancy offers a long time for the cells to age, causing the repair and recovery process becomes weaker. AD is a prevalent disease among the people aged over 65 although; early onset from the 40-50 years has been reported [4].

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There are two forms of AD: familial and sporadic. Familial AD is the early onset caused by genetic factors like APOE4 allele that have strong hereditary links within a family. Sporadic AD is late onset caused by a variety of genetic and environmental factors with ageing being the greatest risk factor [5, 6]. This essay focuses on the sporadic AD.

Alzheimer Disease

What is Sporadic AD?

Sporadic AD is the most common form of AD making upto 97-98% of the cases [7].It is a neurodegenerative disease killing the nerve cells in the brain. Resulting in the loss of memory and confusion that later leads to dementia [6]. Any damage to the nerve cells is detrimental because nerve cells cannot regenerate. The lack of regenerative ability and damage to the nerve cells leads to the permanent loss of functional parts of the brain. The loss of brain function affects the physical and mental wellbeing of the aged person. Damaged nerves cells from the products of AD are located in the central nervous system present in the brain that is postmitotic [8]. Consequently, these cells cannot undergo cell division by mitosis to produce new cells.

How is AD caused?

There are two main commonalities within the brain of AD patients seen in histology of brain tissue: the build-upof amyloid-beta plaques and neurofibrillary tangles[9, 10].Both of these factors are toxic and damage the brain cells causing cell death, which leads to less connectivity within the brain. These factors also physically reduced the size of the temporal and parietal lobes of the brain, which affects auditory and visual processes; hence the common symptom of decline in the cognitive function is seen in AD patients [11].

Formation of Beta-Amyloid plaques

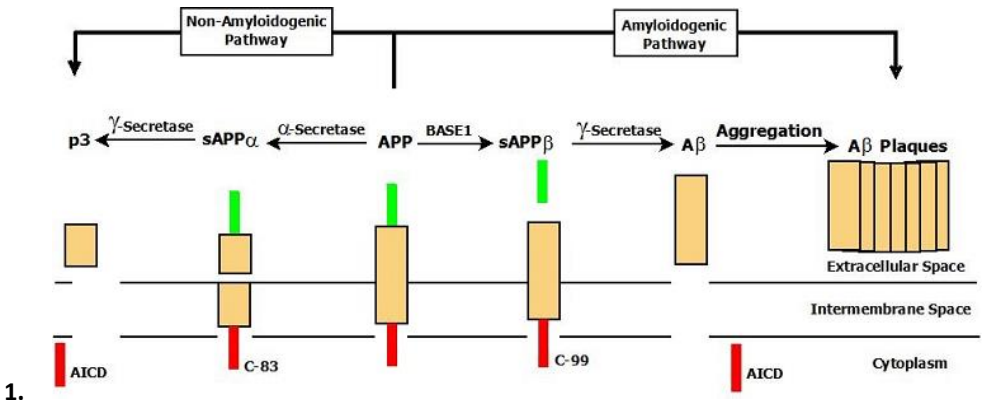

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Fig 1:Breakdown of the amyloid precursor protein (APP) into soluble products through the non-amyloidogenic pathway andinsoluble amyloid beta (Aβ) aggregation through the amyloidogenic pathway [12]

Within nerve cells, there are amyloid precursor proteins (APP) that are extrinsic proteins required for repair of the cell membrane and binding to molecules outside the cells. APP is regularly broken down by protease enzymes: α-secretase and γ-secretase, which hydrolyse peptide bonds to cut the APP into three smaller sections [9, 13].In AD, enzyme β-secretase is produced that cuts the APP in the incorrect position leading to the production of the amyloid beta peptide (Aβ), which is toxic to the nerve cells. The Aβ is able to leave the cell membrane attaching to other Aβ in the extracellular fluid of the brain and aggregating into long insoluble polymers in alpha helix shape stacked on top of each other producing amyloid beta plaques[9, 13].These plaques kill the cells by affecting the synaptic functions between the neurons by inhibiting proper release of neurotransmitter and slowing the action potential, which causes loss of normal function within the cells [14].Plaques also lead to inflammatory responses by the immune system causing macrophages, a type of white blood cell to attack nerve cells in the brain causing irreversible damage to the brain [15]. Therefore, it has become a target to inhibit the enzymes like β-secretase for slowing down the production of Aβ thereby reducing its effects.

Formation of neurofibrillary tangles

Another key feature is that the nerve cells have a cytoskeleton in the axon, which is a pathway of microtubules for the transport of nutrients made from tau proteins required for stabilising microtubules. Tau proteins during AD become hyper-phosphorylated by gaining phosphate group allowing the tau to clump together producing neurofibrillary tangles. The neurofibrillary tangles affect the synaptic communications between neurons causing cell death [9,10, 16].

Why is AD difficult to treat?

AD is difficult to treat because the disease permanently damages the nerve cells so there is no way to restore previous functions unlike other parts of the body where transplants can occur. Aβ can aggregate with a rapid rate of growth through the brain affecting large areas, so it is not localized, therefore cannot be removed by surgery [17]. Drugs produced to get rid of Aβ plaques and neurofibrillary tangles cannot reach the brain in relevant concentration due to the blood-brain barrier. New drugs need to be produced with better permeation through this barrier to breakdown Aβ plaques to be effective against AD [18].Therefore, there is no permanent solution currently for decreasing the rate of

growth for AD other than palliative care measures to offer patients a better quality of life care.

Current treatments used for AD

What is acetylcholine?

Acetylcholine (ACh) is a neurotransmitter released from synapses in normal action potentials found in regions like the hippocampus and temporal lobe, impairing areas of memory formation [19]. The cholinesterase enzyme breaks down the neurotransmitter into choline and ethanoic acid after a nervous impulse has passed through, to return ACh back to the pre-synaptic neuron[20].

What are the current treatments for AD?

The most commonly prescribed drug for treating AD are cholinesterase inhibitors such as donepezil and galantamine for moderate to mild symptoms. As the person ages levels of ACh decreases [21]. The Aβ plaques interfere with synapses and the lowered levels of ACh, decreases communication between cells thereby decreasing short-term memory [22].The cholinesterase inhibitors inhibit cholinesterase enzyme competitively. The inhibitors have a similar molecular shape to ACh so it is able to bind to the active site of cholinesterase enzyme preventing the breakdown of ACh into its substrates. The neurotransmitter can stay longer exciting the postsynaptic neuron for more communication between the nerve cells before being broken down to decrease symptoms of AD. Cholinesterase inhibitors are able to manage the symptoms working in short-term but the body develops a tolerance to cholinesterase inhibitors needing larger doses for the same protective effects and fewer drugs become available to help the patient in later stages of AD [23].

Blood-brain barrier

The blood-brain barrier (BBB) is a selectively permeable membrane, which separates molecules in the blood from the extracellular fluid in the brain. It allows the entry of specific molecules required by nerve cells like water, insulin, glucose and fatty acids by specific transporter proteins and prevents the entry of foreign molecules [24]. Crossing the BBB for producing a cure for AD remains the biggest challenge due to the highly controlled uptake. This is why so many new drugs developed fail, as they cannot enter in sufficient concentration [25].

Structure of BBB

The BBB is made up of endothelial cells in the capillary with tight junctions; these junctions are strands of protein that close the pores in capillaries [26, 27, 28]. For capillaries found in other parts of the body, the pores allow tissue fluid to build up for the exchange of nutrients. In the brain, the build-up of tissue fluid can cause swellings and slow down the diffusion of essential molecules so tight junctions maintain normal function. There are also pericytes, which are cells that wrap around the capillary to maintain the structure and control properties like permeability and blood flow by vasoconstriction and vasodilation[29]. Astrocyte cells surround the brain side of the BBB for transport of molecules from the blood to the nerves cells [28, 30].Therefore, drugs for the AD will be required to be engineered specifically to the BBB cells present and properties of such drugs should be dependent on these cells.

Challenges to entry for drugs into BBB

Molecular weight: Drug transport into BBB is difficult because of the tight junctions, which limit the molecular weight of drugs to approximately less than 400 Daltons (Da) that are able to penetrate into the cells. Most clinical drugs have large molecular weights so they cannot penetrate into the cells through passive diffusion, so they require the use of transporter proteins present on the cell membrane for entry [31, 32].

Changing environment: The environment of the nerve cells and the BBB cells affects the structure of drugs. For instance, lipid solubility affects drug transport because high lipophilicity will allow the molecules to cross through the BBB. The drug's hydrophobic characteristics allow it to cross many cell membranes but within the nerve cells, the aqueous environment requires the drug to be more hydrophilic to have an effect on the cells [31, 32].

Chemical structure: The chemical structure of the drug will be affected by changing the environment of the BBB cells so the molecular structure of the drug needs to be suitable for these conditions. This can be through having the correct proportion of hydrogen bonds for hydrophobic regions, as this will affect the water solubility to have an intended effect on the nerve cells [18, 32].

Efflux pumps: Efflux pumps present on the BBB have a useful purpose in removing harmful molecules from the barrier back into the blood preventing entry of the molecule to damage the nerve cells. However, this will limit the uptake of potential drugs so new drugs needed to aid in the treatment of neurodegenerative diseases could be made to mimic the nature of other absorbed molecules like glucose, which the efflux pumps are not likely to remove [31, 33].For example, P-glycoprotein is an efflux pump that has a broad range of substrates it has an important role in keeping out toxins, this prevents the entry of several drugs making them ineffective [33-35]. Therefore, the structure of the drugs needs to be designed in such a way as not to be similar to the substrates of efflux pumps for removal from the cells.

Immunotherapy

What is immunotherapy?

There are many difficulties for fully active drug for entry through the BBB due to its structure. There has been promising research using immunotherapy to target specific mechanism of AD because there is better uptake to cross the blood barrier and there is a better effect of the drug on the neurons. Immunotherapy is a treatment method using substances, which will lead to an immune response by causing the body immune system to destroy or inhibit the target.

How does Aβ immunotherapy work?

Immunotherapy being researched for AD involves the use of monoclonal antibodies against Aβ plaques as these have shown the greatest results of clearing in preclinical studies on mouse models, showing evidence for this to be further researched on humans. There have been over 9000 patients enrolled in immunotherapy research projects showing the need to explore more about the mechanism of AD that can be targeted for recovery of patients at different stages of the disease[15].Monoclonal antibodies (mAB) are produced by identical B cells from an original B parent cell through mitosis. mAB are highly specific in nature because the antigen-binding site is complementary to the antigen present on their target. This allows antibodies to bind to antigens present on Aβ plaques forming an antibody-antigen complex, which will "tag" the molecule for recognition and clearance by microglial cells within the brain [35]. Microglial cells are found on the nerve side of the BBB, they are macrophages of the brain tissue. They are to be able to move through the nerves to areas of damage to find substances causing inflammation [36, 37]. In a healthy brain, these cells remain dormant and have a role in detecting changes within the interstitial fluid, which surrounds the nerve cells and they assist in the development of the nervous system. These cells can detect the harmful proteins formed during neurodegenerative diseases, which cause inflammation of nerves producing active phagocytic microglial [37]. The microglial have been shown to carry out phagocytosis by engulfing and forming a vesicle around Aβ to digest it by lysozyme (a hydrolytic enzyme), decreasing the build-up of damaging plaques on the nerves [36, 37]. The phagocytic activity of microglial cells can be exploited through antibody treatments because the antibody allows better recognition of Aβ so there can be greater removal by the body's immune system preventing plaque formation [15]. Thus, improving synaptic function and less cell death of neurons, which will lead to improvement in patient's cognition and overall health. In AD, patients suffer from chronic pain requiring them to be on anti-inflammatory drugs because the Aβ plaque deposits cause inflammatory responses to the nerves, which leads to the activation of microglia [38].Additionally, in later stages of neurodegenerative diseases,there is disruption of the BBB causing it to become easily crossed by other types of immune cells like monocytes that attack the Aβ, which would not normally be present in the brain [37].This causes the release of an inflammatory cytokine, which are chemicals that attract more immune cells into the brain causing damage also to the healthy nerve [38].This could suggest that since both microglial and monocytes are part of the innate immune system, the infiltration by monocyte is a necessary process to assist the microglial with the removal of the damaging Aβ so there could be a fault present with the phagocytic ability of the microglial cells to remove Aβ.This is supported because studies have shown that blocking of Toll-like receptors (TLR) such as TLR4, which function in recognition of molecules by binding onto them, which have shown the failure of microglial for phagocytosis [36, 37].

Antibody uptake through BBB

The disruption of the BBB caused in AD could be a possible beneficial property for drug development, as it will allow antibodies to easily cross. Antibodies found in the blood have a very low uptake into the astrocytes, only about 0.1-0.2% of antibodies are absorbed through the BBB to reach the nerves by passive diffusion [35]. The methods for larger uptake of antibodies across the BBB are carrier-mediated and receptor-mediated transport [35]. For uptake by these processes, antibodies have been conjugated. This is by binding antibody molecules with similar to the substrate of transporters for entry without the chemical characteristics of the antibodies like the hydrophobic or electrostatic charges affecting the transfer [24, 39].

Carrier-mediated transport: Carrier-mediated transport (CMT) is the movement of molecules using intrinsic transporter proteins to cross through cell membranes. This movement can be either by facilitated diffusion, which is a passive movement of polar molecules down a concentration gradient or active transport, which uses ATP for movement of polar molecules up concentration gradient in a single direction [18]. CMT allows entry of drugs with larger molecular weight by exploiting the substrates of transporters that have similar structural properties to the drug to be moved across the BBB after a successful collision with the transporter protein. Therefore, there is less effect of the tight junctions allowing drug with a molecular weight larger than 400 Da to cross [40].If the drug has been able to cross into the cell using intrinsic transporter

protein it will be less likely to be affected by efflux pumps because it is a required molecule by the brain due to the conjugated substrate on the antibody. Problems with using CMT are competitive or non-competitive inhibition, which can slow down the uptake of important substrates of the carrier interfering with other mechanisms (18). For example, the Glucose transporter 1(GluT1) protein is an important glucose transporter into the brain and it has a high uptake rate required for cellular respiration [18]. In AD patients, the transporter works less efficiently so producing drugs that utilise GluT1 could inhibit the uptake of glucose needed in cellular respiration leading to cell death. However, effective use of carrier protein has been for the uptake of L-Dopa for the production of dopamine using the L-type amino acid transporter(LAT1) carrier, which is important in the uptake of a wide variety of amino acids into the brain required for protein synthesis [18, 41]. Dopamine is a neurotransmitter that can be used as effective treatments for Parkinson's disease but dopamine cannot itself cross the BBB due to the hydrophilic properties. By forming L-Dopa, which is an optical isomer of dopamine there has been increased permeation of the drug through BBB because L-Dopa is a neutral amino acid able to successfully bind to LAT1 allowing entry into the brain without being affected by the hydrophilic properties [18, 42].Once crossing the BBB, L-dopa is decarboxylated by the enzyme to allow it to form dopamine neurotransmitter for effect [42]. Therefore, transporters like LAT1 could be used in the transport of antibodies by conjugating onto side chains of neutral amino acids to allow uptake then to be released into its active form by enzymes hydrolysing to remove side chains. This is also known as the Trojan horse approach [31].

Receptor-mediated transport: Receptor-mediated transport (RMT) uses the receptors on the cell membrane of the endothelial cells to bind onto. This allows the entry of molecules by endocytosis into the cells, by forming a vesicle around the molecules to allow the substance to enter the cell. This can only occur if the receptor is able to successfully bind to its substrate [40]. The drug will be released by exocytosis, which is the release of the substance from the cell by a vesicle fusing with the cell membrane to secrete out its content into the astrocytes to be distributed around the brain [40]. RMT at the BBB allows entry of larger molecules like iron and insulin so by conjugating antibodies with complementary proteins to the antigen receptors present on the cell membrane of the endothelial cell [24]. The drugs can enter by endocytosis decreasing the limitation of the tight junction for better permeation [40].This is a better method of transportation than CMT because the receptors, which the molecule has to attach, will only be present on that type of cell so the drug can reach a specified location without being absorbed into other cell membranes regardless of where the drug is administered into the body. However, challenges with RMT needs specific proteins, which forms a complex with the receptors for uptake and enzymes present within the cell, could break down the drug before it reaches nerve cells [18].This limits the successful uptake of the drug or could make the drug ineffective.

Drug targets of AD:

Aβ Plaque: Anti-Aβ antibodies can be successful in targeting Aβ plaques because there have been decreased levels of plaque [17]. This has been through the formation of the antibody-antigen complex to allow recognition of damaging Aβ, which has stimulated better receptor-mediated phagocytosis by microglial cells [23]. The anti- Aβ antibodies are able to enhance Phagocytosis due to the binding of the antibody with the Fc receptor, which initiates Phagocytosis on the surface of the microglial cells [15, 36].This suggests that Aβ could have a role in inhibiting microglial phagocytosis in AD patients so antibodies could be an effective method for activation of microglial to clear build-up of future deposits of plaque [36]. On a patient's health, this could allow longer life expectancy because plaques are digested as they are produced so cognitive functions in patients could remain for longer periods.Production of anti-Aβ antibodies to target Aβ has shown results in multiple studies by using transferrin, which is a transporter protein regulating the delivery of iron into the nerve cells[43]. Transferrin protein has a separate transferrin receptor (TfR). Targeted binding of mAB with TfR is a fast process and it does not affect transferrin's binding with iron transport, therefore it can allow uptake of mAB without damaging cell process involving iron or needing to compete with the uptake of iron. Additionally, TfR has a large presence on endothelial cells of the BBB making it a useful target for RMT from the blood to enter the brain [35, 40].However, mAB(s)have presented a challenge because most of the antibodies are transported across the BBB, but they are not well distributed through the brain [35]. This is due to antibodies having a high affinity to receptors that they bind to, which slows the distribution through the brain [43]. Lower concentrations of antibodies are present in the nerves to bind to Aβ. Lowering the affinity of antibodies to receptors using bispecific antibodies can solve this problem [44]. Bispecific antibodies have two different antigen-binding sites where each site can be made complementary to different antigens [45]. In this case, allowing one of the binding sites attaches to TfR

for entry to astrocytes and the other is able to attach to the Aβ on the neuron. The antibody is able to pass across the changing environments from endothelial cells to astrocytes. This has been supported by mice studies where the antibody concentration increased from 2 fold when using high-affinity antibodies to TfR to 6 fold when using low-affinity antibodies allowing better distribution around the brain [35]. In another study, bispecific antibodies have decreased the concentration of Aβ by 47% [44].Suggesting that bispecific antibody could be used as an additional drug with mAB together to decrease Aβ levels.

Antibody inhibition of BACE1:β-secretase (BACE1) has been identified as the main enzyme involved in the cleaving of APP to produce Aβ, BACE1 will form Aβ during its overproduction [9].Drugs produced, as inhibitors for BACE1 have been largely unsuccessful because of the inhibitor's chemical properties like solubility and large molecular size causing lack of permeation through the BBB and lack of selectivity of the drug to attach to the enzyme [46, 47]. Anti-BACE1 antibodies could be used for inhibition of BACE1 by binding to the enzyme and inhibiting it from cleaving APP to reduce the production of Aβ plaques, as there will be less enzyme activity [35]. The antibodies can use the carrier or receptor-mediated transport to travel across the BBB and the use of high-affinity antibodies can selectively target BACE1 [40]. BACE1 is highly present in the brain so this can allow more targeted drug action, as it will be specifically absorbed in these sites. This is beneficial as drugs that have low specificity could be diminished in concentrations by absorption into other cells.BACE1 cannot be completely inhibited because the enzyme is used in several other processes like myelination and synaptic functions, which could negatively affect other parts of the nervous system [48]. Selective inhibition of BACE1with antibodies could produce benefit by controlling excess levels of the enzyme [9]. Hence, there will be an overall decrease in concentrations of Aβ. Anti-BACE1 antibodies can be paired up with anti-Aβ antibodies (as discussed previously), which will decrease the production of new Aβ plaques and allow current plaques on nerve cells to be broken down by phagocytic microglial [35]. However, the results from inhibition of BACE1 have shown mixed responses in clinical studies because the decrease of Aβ is inversely proportional to the antibodies crossed into the brain [35]. This treatment method could be less viable as very high dosage is required to have enough anti-BACE1 antibodies to decrease Aβ, which would not be possible on patients as the toxicity will be too high for treatment.

Challenges & solutions associated with immune-therapy

This essay has assumed on the antibodies being delivered through passive immunotherapy, which is injecting antibodies, not from the body that causes an immune response for targeting Aβ. There are problems associated with this approach because elderly patients have a weaker immune system so there could be a lower response by the body in the activation of microglial cells. On the other hand, there is potential for an autoimmune response, which is the immune cells attacking healthy nerve cells that cannot be controlled [49]. This could worsen the patient's conditions but in current testing, there have been such no incidences seen in the patients [49].Passive immunotherapy will require further testing in clinical trials to find safety limits for the antibodies. A possible solution could be the use of active immunotherapy, which is releasing an antigen of Aβ into the system of the patient to cause immune cells to produce their own antibodies. Active immunotherapy could reduce the high cost of passive immunotherapy because lower dosages of Aβ antigens will be needed to make anti-Aβ antibodies [49]. Passive immunotherapy requires more repeated doses for long periods of time as the antibodies are quickly cleared from the body. Antibodies produced in active immunotherapy are longer lasting and will take longer to reach lower levels [15].The studies have used samples of patients with mild to moderate stages of AD, which has shown improvement in their health but not many late-stage AD studies have been carried out [22, 50]. This may be because the damage to the brain is too large to see an improvement and it could also be difficult to obtain late-stage AD patients to test immunotherapy up on. This infers that earlier detection of AD for immunotherapy will be more effective in slowing the progression of AD. Early diagnosis of AD allows symptoms to be more reversible, which makes them treatable as it can allow the body to adapt to antibodies for the elimination of plaque deposits before microglial cells become inhibited by Aβ [36].

Prospective treatments

Aducanumab antibody: Aducanumab is a current example of a successful monoclonal antibody against Aβ plaques that has reached phase three clinical trials on AD patients [53, 54]. This antibody has shown to be effective in reducing levels of Aβ in its 143 patients sample by increasing dosage levels for 12 months where a majority had lowered levels of Aβ [54]. At its highest doses, the antibody has been able to decrease levels of Aβ below the levels needed for a positive test, suggesting this could be highly useful as a potential treatment [54]. However, these studies have only focused on patients with early stages of AD therefore;

testing on later stages of AD is required to find safe concentrations for patients.

Focused ultrasound therapy: Focused ultrasound therapy is a treatment method in its early stages of clinical trials on AD patients [50]. Ultrasound waves are the of the high frequency of sound waves above human hearing that can be focused at a fixed location forcing the BBB to open for a short time increasing permeability for drugs but it is also reversible to allow the BBB to close [39]. This opening allows the entry of anti-tau antibodies for treating neurofibrillary tangles. These studies have shown cognitive improvement when tested in memory tasks [50]. This treatment shows a possible non-invasive and safer drug delivery method for antibodies used in immunotherapy because ultrasound waves are non-ionising so it will not result in mutations of cells and drugs may require being less conjugated for uptake. Additionally, the ultrasound waves have shown to pass through the skull bone without requiring surgery to remove the bone and have shown not to damage surrounding neurons [55]. This has been evident by using the anti-Aβ antibody, BAM-10, which has shown to decrease the number of plaque in 4 days after treatment on mouse models, showing this treatment having the potential to be viable for patients [50].

Conclusion

With the interest in preventing progression of AD rather than treating its symptoms, immunotherapy shows a useful therapeutic method by targeting the mechanism of AD that forms the toxic Aβ. Drug targets like Aβ plaques and BACE1 show potential for reducing Aβ. Antibodies can be better engineered to cross the BBB and their high selectivity in attaching to Aβ makes them useful for decreasing regions of the brain with the highest density of Aβ plaques. Current trails of the focused ultrasound and aducanumab further reinforce that antibodies targeting production of Aβ have shown results that antibodies are valuable drugs in improving cognition and nerve damage of patients but the absorption of antibodies into the brain tissue remains the biggest challenge in making monoclonal antibodies a suitable treatment method. However, anti-Aβ antibodies studies have proven to show results in mouse models but further clinical trials on patients are required to determine the effectiveness and decrease risks to patients like toxicity levels. Additionally, an important challenge is in identifying patients earlier with biomarkers for AD to allow antibodies to be more effective in preventing AD.

Acknowledgement

Malkhey Verma appreciates the Research Seed Grant from Central University of Punjab, Bathinda, India.

Abbreviations

AD: Alzheimer Disease; APP: Amyloid Precursor protein; Aβ: Amyloid Beta; BBB: Blood-Brain Barrier; Ach: Acetylcholine; Da: Daltons; mAB: Monoclonal Antibody; TLR: Toll-Like Receptors; CMT: Carrier-Mediated Transport; GluT1: Glucose Transporter 1; LAT1: L- Type Amino Acid Transporter; RMT: Receptor-Mediated Transport; TfR: Transferrin Receptor; BACE1: β-secretase; NRG1: Neuregulin 1

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Conflict of Interest: None
Source of Support: Nil