



Exploring Immunotherapeutic Approaches for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a chronic neurodegenerative disorder worldwide that is progressed by the accumulation of highly neurotoxic amyloid-beta ($A\beta$) plaques and neurofibrillary tangles (NFTs) of tau protein within the brain. Despite several traditional treatment methods, there is still a need to explore novel immunotherapeutic approaches for AD. We have summarized the data from the clinical side and the use of various drugs including active and passive immunotherapies. Immunotherapies for treating AD have become the leading therapeutic way and emerging research globally with effective outcomes. The immune system is a complex player in the pathogenesis of Alzheimer's disease. Immunotherapy offers a promising avenue for treating this devastating condition by leveraging the body's natural defence mechanisms. Continued research is essential to unlock the full potential of this approach. Furthermore, we highlighted the impact of phase III clinical trials on intelligence and amyloid elimination in AD subjects treated with lecanemab and donanemab. We also talked about potential contributing variables and possible adverse reactions of anti- $A\beta$ mAbs. In conclusion, we have collected data to explore novel immunotherapies breakthroughs based on tau, $A\beta$, and microglia and their mechanisms of action in AD from published articles and future perspectives.

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1. Introduction

Alzheimer's disease (AD) is a prevalent type of dementia, making up 60-80% of occurrences. It has become a persistent neurological illness that's placing a mounting strain on medical centres worldwide. According to the Global Burden of Disease Study, there were 57.4 million dementia sufferers worldwide in 2019; by 2050, the figure will increase almost 152.8 million ^[1]. The overarching phenomenon known as Alzheimer's disease is generally typified by a gradual decline within numerous intellectual areas, leading to obstacles throughout regular activities within interpersonal, bodily along occupational contexts. Most individuals who experience Alzheimer's disease are aged, yet it is not always an inevitable consequence of growing older. The buildup of neurofibrillary tangles (NFTs), which constitute internal clusters of tau protein, as well as plaques, that constitute external clusters of amyloid- β ($A\beta$), is known as a fundamental component of AD's neurological diseases ^[2]. The drugs (galantamine, donepezil, rivastigmine) and the NMDA receptor antagonists (memantine) have become effective in the treatment of AD patients. Such medications can temporarily lessen symptoms of dementia, but cannot fully stop the progression of the condition along with the onset of symptoms. Additionally, it frequently causes discomfort like headaches, and nausea, alongside drowsiness. Because Alzheimer's Disease represents an intricate illness with many underlying causes, its origins and pathophysiology are still unknown, therefore current single-target, single-action medications are unable to significantly slow down the illness's course ^[3].

But lately, A β immune therapy is attracting interest as a potential method to change the way AD develops. By causing the body's defences to tear apart and eliminate the atypical protein molecules, immunotherapies utilise synthesised amino acids or monoclonal antibodies also known as mAbs, to the A β burden in the central nervous system and limit the progression of the condition. The generation of vaccinations versus specific proteins in AD could become advantageous in combating the illness alongside these inactive immunotherapies [4]. When people with AD are examined neuropathologically, compact accumulations of protein made up of internal NFTs and external A β plaques are found. Examining such individuals uncovers related long-lasting inflammation in the cerebral regions that are impacted. One filament anchoring protein implicated in A β toxicity is tau, which exists within internal neurofibrillary tangles. There's an apparent association between the quantity of this protein in the central nervous system and the cognitive impairment observed in AD patients [5, 6]. An irreparable phenomenon of neurodegeneration and apoptosis in the entorhinal cortex and hippocampal areas is the source of this, which results in apathy, depression, cognitive losses, and diminished cognitive control and supervision. The root cause of the illness is frequently influenced by unfavourable processes that exist together, including disturbance of the blood-brain barrier, elevated oxidative damage, interruption of calcium homeostasis, damage of cellular autophagy, neural inflammation, and neuronal death. The neurovascular linkage prevents interstitial fluid and cerebrospinal fluid from being cleared with its natural quantity [7].

2. Immunotherapies based on A β

The connections between T lymphocytes and glia are a major cause of neural inflammation and death of neurones in Alzheimer's Disease, and the immune system's adaptation plays a vital role in the onset and progression of this illness. The cells that produce antibodies that dwell in the brain, called microglia and astrocytes, are potent controllers of neuroinflammatory reactions in AD [8]. The primary immunological responder in the central nervous system is microglia, which function as phagocytes and antigen-presenting cells [9]. There is significant disagreement over how much microglia contribute to the removal of A β after being activated. The 5-lipoxygenase (ALOX5) pathway is one of the unique inflammatory pathways that have been found to regulate numerous cerebral diseases as a result of recent developments in neuroinflammation investigations. Peripheral T cells can react to brain antigens and to the brain's lymphatic system, which connects with lower cervical lymph nodes and transports immunity-producing cells from the CSF. In AD, CD4+ T helper and CD8+ effector T cells simultaneously clump together in the brain and contribute to the aetiology and advancement of the illness. Nonetheless, the primary APCs in AD belong to microglial cells that exhibit elevated genes and biomarkers linked to T-cell communication, when compared to the peripheral pathways [10]. Additionally, this seems to indicate a decrease of inbuilt immune suppression linked to Alzheimer's Disease, alongside choroid plexus function temporarily affected by Foxp3+ regulatory T cell exhaustion and following recruitment of immunoregulatory cells, including regulatory T cells and monocyte-derived macrophages, in brain spots of plaques pathological research. Ageing modifies such effector and regulatory roles of lymphocytes, and AD development is accompanied by additional immunological symptoms. It has been proposed that leukocyte splitting and telomere reduction are encouraged in AD patients due to neurodegeneration and

the peripheral defence mechanism's concomitant participation [11, 12]. It has been suggested that A β is essential to the pathophysiology of AD. It contributes to the severe cognitive problems seen in AD by causing synaptic damage and neurodegeneration. As a result, A β -targeting tactics may be able to slow the advancement of AD. Anti-A β medications now work primarily through decreasing A β synthesis, inhibiting A β aggregation, and enhancing A β elimination. Many treatments have been studied in recent years for their potential to reduce A β generation and prevent A β clusters. However, because they have all fallen short, it should be reevaluated whether or not A β remains a vital therapeutic target and merits more research. As the overall major contributory factor of the neurodegenerative mechanism in AD is A β buildup, expediting its elimination could be a good idea. As a result, immunotherapy has emerged as the main area of investigation to facilitate A β removal and has significantly influenced studies on anti-A β treatments [13].

At this point, vaccinations and exogenous antibodies either passive or active immunotherapy, represent the majority of sophisticated anti-A β immunotherapies. By exposing our immune systems to A β or its parts, active immunisation increases the production of endogenous defences against A β . The reduction of A β accumulation in the brains of PDAPP mice was initially observed to be possible through active immunisation against complete A β [14]. Following it, AN1792, the vaccine which targets complete A β , was created and put through laboratory testing. Whereas 6% of the enlisted individuals who had moderate-to-severe AD experienced T cell-based meningoencephalitis, which led to the research tests' termination. The subsequent series of vaccinations, like CAD106, originated lacking a T-lymphocyte region to lessen an overreaction by the body's defences. Active immunotherapy offers the benefit of temporary medication delivery combined with persisting antibody molecules at low prices, whereas it additionally carries the risk of unpredictable immunological reactivity and side effects, especially within older patients [15]. Many efforts have been made to increase A β removal through passive immunotherapy employing humanised monoclonal or multi-clonal immune system antibodies as a result of the limited responsiveness of vaccinations and the appearance of T cell-dependent undesirable responses. While passively administered immunotherapy guarantees reasonably stable immunoglobulin levels, this generally comes alongside additional side effects like vasogenic swelling and cerebral amyloid angiopathy accompanying microhemorrhages. Antibody opsonisation of the antigen, resulting in complement signalling and macrophage phagocytosis, antibody-mediated peripheral decrease in A β in favour of A β effusion via the neurological system, antibody-catalyzed alteration of the supplementary framework of A β monomers to prevent the synthesis of oligomers and Fc receptor-mediated discharge of antibody-antigen complexes throughout the blood-brain barrier are broadly accepted as means of inactive immunization [16].

3. Active immunotherapy Strategies

The initial anti-A β vaccination to be therapeutically examined was AN1792. This completely synthesised A β 42 has a booster called QS-21. 19.7% of the individuals receiving therapy with AN1792, who had elevated anti-AN1792 IgG levels, had immune responses in the stage II A clinical investigation. Nevertheless, such distinction occurred

solely in the antibody responders, even while AN1792 therapy decreased A β deposits and had a beneficial impact on both the neuropsychological test battery (NTB) score and cerebrospinal fluid tau amounts [17]. Additionally, 6% of handled individuals experienced T cell-mediated meningoencephalitis as a consequence of the AN1792 via injection, which prompted the therapeutic research's discontinuation. The antibody responders identified during the earlier stage II A trials continued to have minimal but noticeable anti-AN1792 antibody levels, contributing to the longer-term functional advantages along with a decline in functioning. This information was discovered in subsequent monitoring studies [18]. N-terminal A β 1-6 represents a B-cell epitope found in a vaccine amilomotide (CAD106), which stimulates the production of anti-A β antibodies in the absence of an A β -specific T-cell response. CAD106 demonstrated a satisfactory antibody response and a good secure description, according to the phase I study results. Phase II studies (II A, II B) indicated a suitable trade-off between tolerance and antibody response [19]. Unfortunately, CAD106, the first vaccination to reach a phase II/III trial, caused unexpected alterations in body mass index, brain size, and intellectual performance, forcing an earlier research termination. UB-311 is made up of 2 artificial A β 1-14-targeting sequences that are coupled to distinct helper T-cell peptide epitopes as B-cell epitopes. To decrease T-cell inflammatory responsiveness and increase immune response, the Th2-biased administration strategy is used. Due to an ultimate response rate of 100% as well as an on-target immune response, UB-311 showed promise for improving cognition in sufferers having early-to-mild AD, according to phase II research findings [20].

4. Passive immunotherapy

Humans IgG1 monoclonal antibody Aducanumab (BIIB037) forms a long conformational bond with the N terminus of A β . It goes after A β aggregates, which include insoluble fibrils and soluble oligomers. Amyloid PET (positron emission tomography) standardised absorption ratio composite rating with a significant decrease in sufferers receiving treatment with aducanumab in the phase Ib randomised study PRIME, particularly in individuals administered via 10 mg/kg aducanumab at 54 weeks. In those suffering from preliminary or moderate AD, brain amyloid load dropped in a manner that was time- and dose-dependent [21]. Humanised lecanemab (BAN2401) selectively targets accessible accumulated A β alongside exhibits action against oligomers, protofibrils, and inert fibres. The brain plaques containing amyloid declined in the BAN2401-G000-201 phase II trial, despite not meeting the 12-month main target. Numerous therapeutic and biomarker outcomes demonstrated durable clinical recovery at the greatest dosage of 10 mg/kg biweekly. Through a duration of eighteen months, there was a dose-dependent

drop in the amyloid PET SUVR value and a clinical deterioration according to the AD Composite Score (ADCOMS) and ADAS-Cog14. A distinction in CDR-SB deterioration within the lecanemab and placebo-treated individuals was considerable at twelve months, yet insignificant at eighteen months, which makes it a puzzling conclusion [22]. The Bayesian sensitivity analysis showed that fortnightly doses of 10 mg/kg of lecanemab reduced intellectual degradation more in APOE4 carriers than in non-carriers when compared to control. When contrasted to the control group, CSF biomarker tests revealed a rise in A β 42 and a fall in p-tau; however, outcomes on total tau varied within twelve and eighteen months. It is noteworthy that lecanemab acceptance was demonstrated by the ARIA-E occurrence, which was 9.9% at 10 mg/kg in the general populace and 14.3% in APOE4 carriers. Evaluating a prolonged period of protection, tolerance, and potency of lecanemab for initial Alzheimer's disease a phase III trial called Clarity Alzheimer's Disease is now in progress. Further phase III trial, called AHEAD 3-45, was carried out to evaluate the security and effectiveness of lecanemab in early Alzheimer's disease sufferers. Its main objective was to ascertain the alteration from the beginning to the final Preclinical Alzheimer Cognitive Composite 5 scores at 216 weeks of intervention [23].

Human IgG1 monoclonal antibody gantenerumab (RO4909832) adheres to accumulated A β through a strong attraction plus promotes A β elimination through phagocytosis controlled by Fc receptors. For those suffering from hereditary Alzheimer's disease, gantenerumab was shown to have failed to reach the main objective across a phase II trial. Subsequently, a second phase II trial was conducted in people having alterations linked to symptoms that begin with Alzheimer's disease called DIAN-TU-001 [23]. Administration of gantenerumab drastically lowered A β plaques, phospho-tau181, and total tau in the CSF, and mitigated elevated levels of neurofilament light chain, yet did not affect psychological measures [40]. Oedema associated with imaging abnormalities attributable to amyloid occurred in 19.2% of the individuals. Because of the above results, it was thought that a greater gantenerumab dosage was required for clinical success. Two phase III trials, called GRADUATE 1 and GRADUATE 2, are now in progress to examine the risks and benefits of gantenerumab in a wider spectrum of Alzheimer's disease sufferers who have not generally been triggered due to gene mutations [24].

The overall summary of the action of active and passive immunotherapies in treating Alzheimer's disease, their basis and mechanism of action, possible risk factors, Outcomes, and prospects are given in Table 1.

Table 1: Summary of the action of active and passive immunotherapies

Immunotherapy Type	Basis of Treatment	Mechanism of Action	Possible Risk Factors	Outcomes	Future Perspectives
Active Immunization	Stimulation of the immune system	Induces production of antibodies against A β ; promotes clearance of A β plaques	Brain inflammation, other autoimmune reactions	Mixed results in clinical trials; some evidence of A β reduction	Continued research with improved vaccine designs, focuses on specific immune responses
Passive Immunization	Direct administration of antibodies	Binds to A β , facilitating clearance by immune cells	Infusion-related reactions, potential for increased brain inflammation	Some success in reducing A β levels, but limited cognitive benefits	Further development of more effective antibodies, combination therapies with other treatments

5. Immunotherapies based on tau protein

NFTs are an additional prominent feature of Alzheimer's disease and Tau is an intracellular protein which binds to tubulin within proper station polymerisation, anchoring microtubules. Nevertheless, hyperphosphorylated tau in Alzheimer's disease possesses a decreased capacity to connect with microtubules, which ultimately results in the development of clusters and NFTs. Notably, among individuals with Alzheimer's illness, the tau protein seems to have a stronger correlation with the degree of memory loss than A β , suggesting that therapies aimed at tau could be effective. Prohibiting aberrant tau phosphorylation, and avoiding tau accumulation, while encouraging the elimination of tau clusters are there are three primary known anti-tau tactics [25]. Immunotherapies comprise the majority of anti-tau medicines presently undergoing clinical studies. Activated vaccinations consisting of AADvac1 and ACI-35 along with passively immunotherapeutic immune cells including semorinemab, gosuranemab, and BIIB076 have been developed after tau immunotherapy had initially shown to be efficient in the JNPL3 mice model. In animal models of Alzheimer's disease, each one of them exhibits noteworthy therapeutic outcomes, and the majority has been investigated in clinical settings. This has been demonstrated that tau immunologic agents with modest supplements can effectively lower pathogenic tau concentrations without producing substantial unfavourable immunological reactivity [26].

Neurofibrillary tangles, which undergo formation when tau protein aggregates, can be an additional significant pathogenic characteristic of Alzheimer's disease besides amyloid plaques. The MAPT gene encodes a protein called tau, which is linked with microtubules. There are various 6 isoforms of tau in the body's brain and spinal cord, with the most extensive one comprising 441 amino acids. The above isomers remain intact in the proline-rich domain (PRD) at positions 151–243 while varying in the N-terminal acidic domains and the C-terminal microtubule-binding site [27]. Tau is extensively soluble within the average human brain and is mostly found in neurones. This interacts with tubulin and assists in microtubule construction, controls microtubule stabilisation, as well as plays a role in the transportation of axons. Within Alzheimer's disease pathology settings, tau phosphorylation rises dramatically, causing tau to dissociate with microtubules and then subsequently assemble into filaments, oligomers, and ultimately Neurofibrillary tangles. It is believed that accelerated tau accumulation, synaptic malfunction, and neuronal death all are significantly influenced by phosphorylated tau [28]. Although a precise reason for tau hyperphosphorylation is unknown, this might be associated with the unbalanced functioning of phosphatases which means protein as an enzyme called 2 (PP2A) and kinases like glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinase 5 (CDK5). This was recently demonstrated that both the cerebrospinal fluid and bloodstream of people suffering from Alzheimer's Disease have elevated levels of multiple phosphorylated tau different species, including P-tau181, P-tau217, and P-tau231, two decades before the beginning of indications. This is remarkable to note that tau deposition and cognitive impairment intensity are more strongly correlated with PET assessments instead of amyloid depositions [29]. The idea of tau causes A β -induced neurotoxicity and is supported by several rows of data. When split by δ -secretase, tau (1–368)

along with APP (586–695) particles it contribute to BACE1 excessive expression alongside A β production. In hAPPJ20 AD model mice, endogenous tau reduction prevented excitotoxin-induced neural disorder, yet it had no impact on A β accumulation. In APP/PS1 mice, tau elimination prevented neuronal and synaptic degeneration and decreased the amount of amyloid plaque. Furthermore, tau must be present for the limiting impact of A β on the transportation of axons. When combined, regulating tau concentrations may help to mitigate Alzheimer's disease neurodegenerative pathogenesis. It is important to remember because tau performs regular bodily tasks [30].

6. Immunotherapy based on microglia

It is believed that microglia are involved in inflammatory processes and the neuro-immune reaction in the brain and spinal cord. It is believed that receptors like TLR-4 on the outermost layer of microglia recognise A β and phosphorylated tau protein as damage-associated chemical sequences, which trigger the secretion of inflammation-associated factors in Alzheimer's disease brains. The development of A β plaques and tangled neurofibrillary fibres is subsequently accelerated by the inflammatory variables, resulting in a vicious loop that worsens the degenerative state [31]. The rate at which tau extends throughout Braak stages is determined by an association between A β and activated microglia, as demonstrated by the latest PET (positron emission tomography) analysis including 130 participants. This finding emphasizes the close relationship between microglia and the pathogenic proteins in the degenerative phase of Alzheimer's disease. Furthermore, an elevating proportion of genome-wide association research has shown that several Alzheimer's disease susceptible genes, including TREM2, have a significant impact on microglia. This suggests that antibodies may be able to concentrate on those molecules to modify microglial operation and the brain's neuro-immune mechanism [32].

One important receptor that the brain's microglia make specifically is TREM2. It has been determined that certain TREM2 mutations raise the threat of Alzheimer's disease with a later initiation. Presently, in an Alzheimer's disease animal model, microglia expansion may decrease Alzheimer's disease pathological conditions through the activation of the TREM2 receptor's downward signalling by a TREM2 agonistic antibody that binds the external region of TREM2. A couple of TREM2 antibody-based research investigations have recently started in light of the promising preliminary findings [33]. A humanised monoclonal IgG1 antibody called AL002 was created in collaboration with AbbVie and Alector to attack TREM2. Through its interaction with the microglial receptor TREM2, AL002 stimulates the expansion of microglia by enhancing the phosphorylation of TREM2 subsequent effector Syk thus activating TREM2 signalling. A phase II clinical trial is currently being conducted to investigate the potential benefits of daratumumab delivery for people suffering from mild-to-moderate Alzheimer's disease [34]. Because of the involvement in inflammatory processes and AD-associated stimulation of microglial cells, the microbiota of the digestive tract is currently attracting more interest. Sodium oligomannate is an acidic linear oligosaccharide combination made from marine brown algae extraction. Sodium oligomannate is not seen as a conventional immunotherapeutic treatment; nonetheless, controlling gut

microbiota including the relationship between the gut and the brain, lowers neurological inflammation and microglial stimulation, which afterwards delays cognitive decline. Within North America, Europe, and Asia, a phase III multinational test for sodium oligomannate has just begun among people with moderate to severe Alzheimer's disease [35].

7. The limitations and challenges of immunotherapies

Immunotherapies show promise as an approach for Alzheimer's disease, yet there are potential drawbacks along with consequences. Negative outcomes or therapeutic reactions are a serious issue, as outlined regarding the vaccination AN1792. Immunotherapy administration may be overreactive, which could harm rather than benefit the sufferer [36]. An overreactive immune system reaction in Alzheimer's disease patients may cause additional neurodegeneration through several different mechanisms. Like microglial and astrocyte transmission, overproduction of inflammatory cytokines may cause more neuroinflammation, which in turn may worsen the illness condition. Additionally, autoreactive responses from T cells are a critical precautionary measure that needs to be watched out for and can emerge. It is also necessary to take into account various issues regarding the effectiveness of immunotherapies. Immunotherapies are appealing partly because they use the immune system of the individual to combat their illness [37]. On the other hand, those suffering from serious cognitive impairment are usually older and have impaired immune responses, which can be a result of comorbidities or ageing. Consequently, immunotherapy might go wrong in several ways. For instance, there is a greater chance that CD5+ B cells will produce auto-antibodies, there is a reduction in the quantity and function of naïve CD4+ and CD8+ T cells, and the capacity of the bone marrow to produce new B cells is compromised. Moreover, age-associated immunosenescence may make immunotherapy less effective at eliciting pathogenicity and could potentially lead to adaptation [38].

The prospect that neurodegeneration in Alzheimer's disease can be delayed or altogether avoided by boosting A β removal is raised by the authorisation of the human monoclonal A β antibody aducanumab, however, it is currently uncertain how near the illness is to being completely treated [39]. Immunotherapy is without a doubt one of the most cutting-edge therapeutic approaches currently available for the cure of Alzheimer's disease, however, there still exists a few things to consider. Initially choosing the right objectives is an essential preliminary phase in the creation of disease-modifying therapies for Alzheimer's disease. For a long time, the A β and tau hypotheses have been put forth, and both of these proteins are also linked to other postulated processes including neuroinflammation [40]. Nonetheless, there is disagreement over the connection between mental ability and the production or accumulation of these two proteins. Thus, it is essential to further define A β and tau as viable objectives for treating Alzheimer's disease medications that modify the disease or to take into account additional significant components that promote the development of AD [41]. Several unusual strategies for immunotherapy, including TREM2, CD38, and TNF- α , have been investigated in clinical investigations. Recent developments in spatially transcriptome sequence and single-cell RNA sequence will help immunotherapy locate and concentrate potentially

beneficial drugs. Like A β immunotherapy, the effectiveness of tau antibodies or vaccinations can vary depending on several circumstances. The tau epitope and the place where it acts (inside of cells or outside of cells) could represent the two very significant factors within them [42]. Understanding the type of tau that is present within cells of neurones and the type that diffuses within cells around them to initiate tau pathology in Alzheimer's disease is crucial. Anti-tau antibodies can associate with exterior tau to stop the progression of tau disease, or they can penetrate neurones in the cerebral cortex and attack internal tau proteins. According to reports, tau segments spanning 150–250 peptides make up the majority of CSF tau, and this evidence suggests antibodies targeting these amino acids can be beneficial in stopping the propagation of external tau. An increasing amount of research indicates the possibility of variations could occur in the aetiology and intensity of Alzheimer's disease sufferers, and that precise identification and tailored therapy might be more advantageous for Alzheimer's disease individuals [43]. Most people agree that in Alzheimer's disease brains, pathogenic A β develops sooner than tau. A β immunotherapies, like aducanumab, have a higher probability to be advantageous at the beginning or initial stages of Alzheimer's disease with few clinical manifestations due to the distinct resulting instances and positions of A β and tau throughout Alzheimer's disease development. In contrast, the tau immunisation approach could be advantageous in minimising cognitive impairment in sufferers with modest to serious Alzheimer's disease [44]. Furthermore, individuals with early-onset or moderate Alzheimer's disease comprise the majority of individuals in clinical studies involving both tau and A β immunotherapy, which emphasises the importance of prompt detection and intervention in Alzheimer's disease therapeutic approach. However, early detection of Alzheimer's disease has been hampered by the absence of a reliable biomarker or intellectual score. Initial detection and good therapies are critically needed [45]. Unquestionably, aducanumab's FDA authorisation has generated disagreement, but its human monoclonal A β antibody introduces the hope that A β elimination could stop or slow down Alzheimer's disease neurodegeneration. It will further substantially advance the investigation and creation of additional Alzheimer's disease immunotherapies. In an attempt to create advanced vaccinations and antibodies, investigation is being done to address issues with immunotherapy for Alzheimer's disease, such as targeting selection, negative consequences of drug administration, and preliminary Alzheimer's disease detection. The creation of novel immunotherapeutic medications for Alzheimer's disease would be made possible by a settlement of such problems [46].

8. Conclusion and future perspectives

Since A β is a very well-researched pathological characteristic of AD pathogenesis, tau pathology and neuroinflammation are receiving greater consideration as potential areas for therapy. That's because numerous current treatment efforts aimed at targeting this peptide have frequently flopped in clinical trials. One potential approach to cure AD is immunotherapy that targets the A β load. Insufficient immunotherapeutic techniques, improper models, insufficient pathogenic objectives as well as poor designs for clinical trials could all be to blame for it. Preliminary studies on Alzheimer's disease probably underrated two critical

aspects: the utility of the present mouse models of Alzheimer's disease and the immunological distinctions between individuals and mice. Presently under investigation, the precise role played by the various activated microglia subgroups in Alzheimer's disease is not well understood. To completely understand the contribution of microglia in Alzheimer's disease, several parameters must be taken into account, including age, gender, different species, molecular diversity, well-being, and interactions within the periphery. This represents a discipline of investigation that is both intriguing and hard, with the potential to define novel therapy options as well as ultimately lessen the financial and social consequences of this life-threatening condition. Potent vaccinations that stop or delay Alzheimer's disease could be a practical as well as cost-effective way to prevent paying astronomical expenses for therapy.

An additional promising treatment option for Alzheimer's disease is gene therapy. The biggest inherited vulnerability component for Alzheimer's disease is ApoE ϵ 4. Lowering ApoE ϵ 4 concentrations has been demonstrated in research to lessen A β pathology in mice with A β amyloidosis. In APP/PS1 mice, medication using ASOs that attack ApoE ϵ 4 before plaque buildup can significantly affect when A β pathology starts. Furthermore, in tauopathic model mice, therapy aimed at ApoE ϵ 4 markedly maintained synaptic density and decreased neuroinflammation. Adeno-associated virus (AAV)-based gene therapy that targets APOE, known as LX1001, has just started a phase I/II clinical trial (NCT03634007). As regards the findings presented at the 15th CTAD in 2022 by Lexeo Therapeutics, the presence of APOE2 in ApoE ϵ 4 carriers changed the concentrations of biomarkers linked with Alzheimer's disease, including P-tau. Therefore, for sufferers of Alzheimer's Disease who contain ApoE ϵ 4, lowering the ApoE4 level or modifying the activity of other APOE variants may provide tailored treatment choices.

Another possible therapy option for Alzheimer's disease is stem cell transplantation. Neural stem cells (NSCs) grafted into injured cholinergic neurones can repair them. preliminary study has shown that newly born functioning neurones can improve mental abilities by forming novel synaptic relationships with the host's leftover neurones. In addition, NSCs can secrete neurotrophic agents like BDNF to promote synaptic density, activate microglia for immunological control, and defend neurones by releasing growth regulators and anti-inflammatory cytokines. It has been demonstrated that NSC transplants into Parkinson's disease patients' brains are harmless. Disease-modifying treatments for Alzheimer's disease that target neuroinflammation have drawn greater curiosity in recent decades. Microglia help draw T lymphocytes inside the brain of tauopathic mice. T cells then release IFN γ , which may induce the development of CD11c+ microglia. Probably in a manner, these triggered microglia increased tau pathology and neurodegeneration by inducing responses of inflammation and facilitating the delivery of antigen to CD4+ T cells via T cell receptor. In tauopathic mice, suppression of T cells or microglia reduced neurodegeneration. In brief, elucidating the intricate pathogenic pathways is critical to developing efficacious therapies for Alzheimer's disease. In years to come, Alzheimer's disease sufferers may benefit from additive or synergistic effects through early recognition, prompt assistance, multidrug combinations, and multimodal therapies.

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Faiza Shahzad – Literature Extraction, Manuscript Writing, Concept of the Data

Quratulain Ashfaq – Literature Extraction, Re-evaluation, Finalizing

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Bilal Atiq – Manuscript Writing, Re-evaluation

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The author declares that they have no conflict of interest.

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