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Analytical Methods for Donanemab: A Therapeutic Antibody for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, marked by memory loss, cognitive decline, and functional impairment. Its pathology is characterized by extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles formed by hyperphosphorylated tau, synaptic loss, and chronic neuroinflammation. Genetic factors, including mutations in APP, PSEN1, and PSEN2 and the presence of the APOE ε4 allele, increase disease risk, particularly in early-onset AD.

Despite extensive research, current therapies mainly offer symptomatic relief. Donanemab, a monoclonal antibody targeting pyroglutamate-modified Aβ, represents a disease-modifying approach by promoting amyloid plaque clearance in early Alzheimer's disease. Clinical trials demonstrate significant amyloid reduction and modest slowing of cognitive decline, with amyloid-related imaging abnormalities as key safety concerns. Biomarker-driven analytical methods, including edema and microhemorrhages, requiring careful monitoring.

Combining amyloid-targeted therapy with interventions addressing tau pathology, neuroinflammation, and vascular dysfunction represents a promising multi-modal approach to more effectively modify disease progression.

Keywords: Alzheimer's Disease; Donanemab; Elisa; Mass Spectroscopy; Neurodegenerative Disorder

1. Introduction

Alzheimer's disease: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and affects millions of individuals globally. AD is linked to memory loss and cognitive decline that gets worse with age [1]. Alzheimer's disease (AD) is the most common type of dementia in the elderly; other varieties include vascular dementia, Lewy body dementia, and frontotemporal dementia. AD mostly affects the hippocampus and prefrontal cortex as it advances, impairing cognitive abilities. Extracellular buildup of amyloid-β (Aβ)1–42 peptides and intracellular neurofibrillary tangles (NFTs) made up of phosphorylated tau proteins and Aβ oligomers have been documented in studies. As the illness develops, synapse loss and cognitive impairment result. Tau proteins are usually phosphorylated at about ten locations in healthy individuals. Tau phosphorylation, however, reaches 40–45 sites in AD patients. As a result, hyperphosphorylated tau is carried to many regions of neurons, including the soma and dendritic spines, breaking the synaptic connections between them since it can no longer attach to microtubules. Three main genetic mutations linked to Early-Onset Alzheimer's Disease (EOAD) have been found through molecular and genetic research in AD patients [2,3,4,5].

Neuropathologically, this progressive disease is marked by intracellular neurofibrillary tau tangles, extracellular amyloid-β (Aβ) plaques, and persistent neuroinflammation that results in neuronal death and synaptic dysfunction. The

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complicated and multifaceted character of AD pathophysiology has hindered the discovery of really disease-modifying treatments despite intensive research efforts. The need for alternative treatment techniques is highlighted by the limited clinical efficacy and considerable side effects of current therapeutic approaches, including recently licensed anti-amyloid immunotherapies [6]. Memory loss, aphasia, agnosia, visuospatial impairment, deficiencies in critical thinking and computation, as well as personality and behavioural abnormalities, are the main clinical manifestations. Many older persons experience growing social isolation and become totally dependent on others as a result of AD and dementia, which are affecting an aging population [7].

Key Pathological Mechanisms involved in Alzheimer's disease

- Amyloid-β (Aβ) Plaques: Extracellular deposits of aggregated Aβ peptides — especially Aβ42 — are a hallmark of AD. These plaques disrupt synaptic function and activate immune responses in the brain.
- Tau Neurofibrillary Tangles: Intracellular accumulation of hyperphosphorylated tau forms neurofibrillary tangles (NFTs). These tangles impair axonal transport and lead to neuronal loss.
- Chronic Neuroinflammation: Persistent activation of microglia and astrocytes contributes to synaptic dysfunction and neuronal damage. Genetic risk factors (e.g., APOE ε4, TREM2) influence neuroimmune responses.
- Synaptic Dysfunction & Neuronal Loss: Aβ, tau, and inflammatory processes collectively reduce synaptic
- connections and lead to cognitive decline.
- Metabolic & Other Dysfunctions: Mitochondrial impairment, autophagy-lysosomal dysfunction, and gut-brain axis dysregulation further exacerbate pathology [8].

The fundamental cause of Alzheimer's disease development consists of Aβ plaques which collect coupled with hyperphosphorylated tau proteins in addition to neuroinflammation and mitochondrial degeneration and disintegration of the blood-brain barrier. Using MRI technology, PET scans, cerebrospinal fluid biomarkers, and novel blood-based detection methods, clinical diagnosis can be made early.

A possible therapeutic strategy is immunotherapy, which uses antibodies to help the Aβ peptide be cleared. Soluble equilibrium, phagocytosis, or blockage of amyloid seeding have been proposed as the three primary modes of action for Aβ immunotherapy. Antibodies neutralize soluble Aβ and change the equilibrium to favor dissolution, which is the basis of the soluble equilibrium mechanism. It is suggested that this method of action occurs in both the central and peripheral compartments Antibodies must enter the central nervous system (CNS) in order to engage deposited amyloid (opsonization) and enable microglial-mediated phagocytosis of the plaque [9].

2. Neuropathology of Alzheimer's Disease

Positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients, are one of two types of neuropathological changes in AD that provide information about the disease's progression and symptoms.

Negative lesions (caused by losses) that exhibit significant atrophy as a result of a loss of neurons, neuropils, and synapses. Besides, other causes might cause neurodegeneration such as neuroinflammation, oxidative stress, and damage of cholinergic neurons [10].

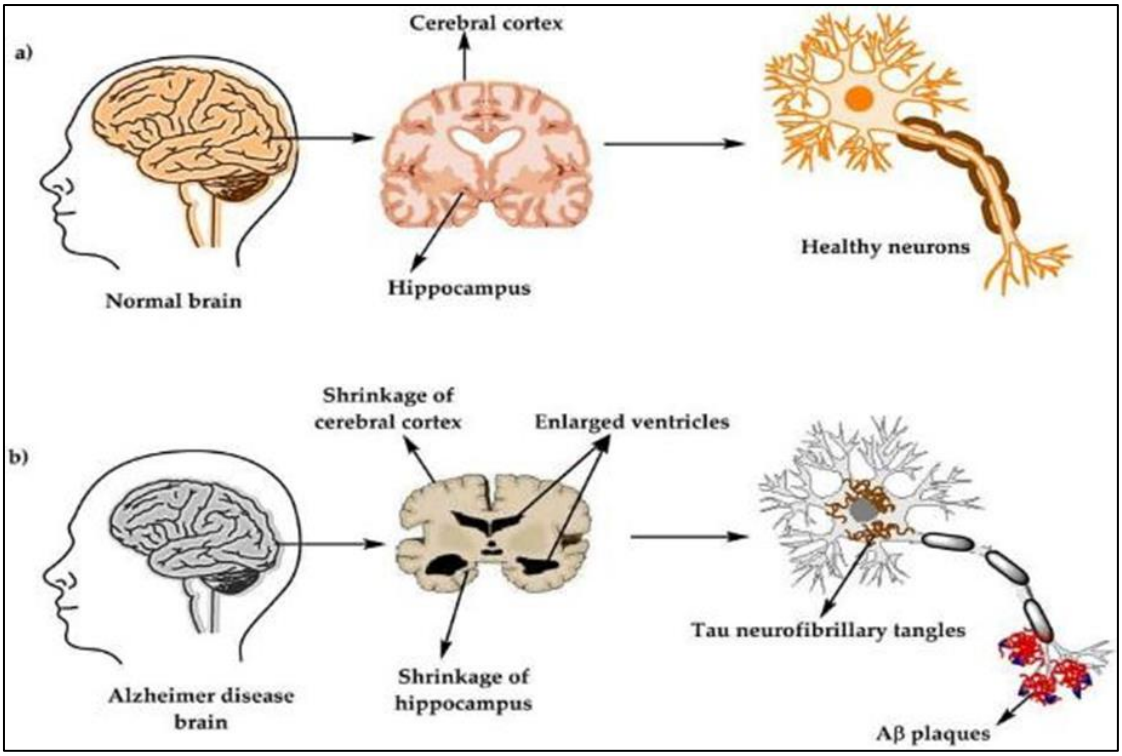

Figure 1 Neuropathology of Alzheimer's Disease

3. Stages of Alzheimer's Disease

Alzheimer's disease clinical phases are divided into four categories:

- Pre-clinical or pre-symptomatic, which can continue several years or longer. This stage is distinguished by modest memory loss and early pathological changes in the cortex and hippocampus, but there is no functional impairment in everyday activities and no clinical signs or symptoms of Alzheimer's disease.
- The mild or early stage of Alzheimer's disease, where various symptoms begin to occur in patients, such as problems in the patient's everyday life with a loss of attention and memory, disorientation of place and time, a change in mood, and the development of depression.
- Moderate AD occurs when the illness extends to cerebral cortex areas, resulting in significant memory loss, difficulty recognizing family and friends, loss of impulse control, and problems reading, writing, and speaking.
- Severe AD or late-stage, which involves the spread of the disease to the entire cortex area with a severe accumulation of neuritic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where patients cannot recognize their family at all and may become bedridden with difficulties swallowing and urination, eventually leading to the patient's death due to these complications [11,12].

4. Causes and Risk Factors for Alzheimer's Disease

Alzheimer's disease is thought to be a complex disease caused by a variety of risk factors (Figure 2), including advancing age, genetics, head injuries, vascular diseases, infections, and environmental variables.

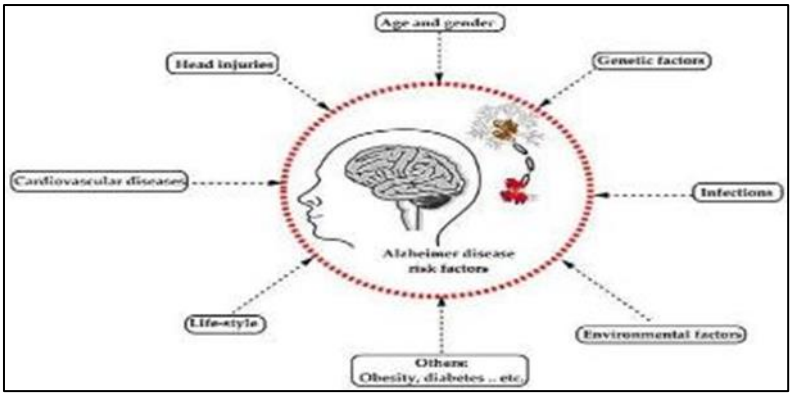

Figure 2 Risk factors of Alzheimer's Disease

The cause of pathological alterations in Alzheimer's disease (Aβ, NFTs, and synaptic loss) remains unknown. Several hypotheses have been proposed as a cause for Alzheimer's disease, but two are believed to be the main cause: some believe that impaired cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. However, there is currently no recognized explanation to explain the AD pathophysiology [11,12].

5. Therapies for Alzheimer's Disease

Despite being a major public health issue, only two drug classes are currently approved for AD treatment

- Acetylcholinesterase inhibitors (AChEIs)
- NMDA receptor antagonists.
- AChEIs increase acetylcholine levels by inhibiting its breakdown, while NMDA antagonists reduce glutamate-induced calcium overload that leads to neuronal damage. However, both therapies only provide symptomatic relief and do not halt or cure the disease [10].

5.1. Donanemab

Donanemab is described as a humanized IgG1 monoclonal antibody that specifically binds to a form of amyloid-beta (Aβ) — the peptide that aggregates into plaques in the brains of people with Alzheimer's disease. It targets a modified form called pyroglutamate-modified Aβ (pGlu3-Aβ), which is highly prone to aggregation and is abundant in mature amyloid plaques. By binding these plaques, donanemab facilitates immune-mediated clearance, helping reduce amyloid burden in the brain. Like other anti-amyloid antibodies, donanemab treatment is associated with amyloid-related imaging abnormalities (ARIAs). These include ARIA-E (edema/swelling) and ARIA-H (micro-hemorrhages) seen on brain MRI, which require careful monitoring.

Donanemab had received full approval from the U.S. FDA (as of April 2025) based on the Phase III trial results. It also notes that regulatory applications (e.g., to the European Medicines Agency) were under review or pending at the time of writing.

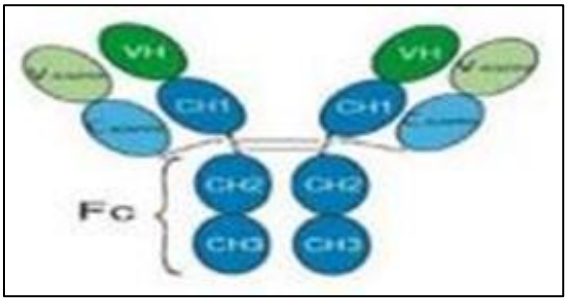

Figure 3 Chemical structure of donanemab

Figure 4 Donanemab Injection

5.2. Donanemab in Alzheimer's disease

5.2.1. Amyloid reduction:

Donanemab produced a rapid and robust decrease in brain amyloid plaques, detectable as early as 12 weeks, measured by florbetapir F18 positron emission tomography (PET) using the Centiloid scale.

Single doses (10–40 mg/kg) showed dose-dependent plaque reduction by Week 24; higher doses caused larger reductions.

Multiple dosing (e.g., 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks) resulted in greater amyloid reduction, with some patients achieving complete amyloid clearance (<24.1 Centiloids) within 24–36 weeks.

Pharmacokinetics & immunogenicity:

Donanemab exhibited dose-proportional pharmacokinetics, with an estimated elimination half-life around 9.3 days at 20 mg/kg.

Treatment-emergent anti-drug antibodies (ADAs) developed in most patients (>90%), but they did not significantly affect pharmacokinetics or the extent of amyloid reduction.

5.2.2. Safety

Donanemab IS generally well tolerated.

The most common adverse events were amyloid-related imaging abnormalities (ARIA) — particularly vasogenic cerebral edema (ARIA-E) and cerebral microhemorrhages (ARIA-H) — which are characteristic of anti-amyloid antibodies.

Plaque reduction and slowed clinical decline have been demonstrated, it remains unclear whether donanemab leads to meaningful long-term clinical improvement, and further research is needed to understand how amyloid clearance interacts with tau pathology and overall disease progression [15].

Although donanemab received Breakthrough Therapy designation from the U.S. FDA in June 2021, an application for accelerated approval was rejected in January 2023 due to insufficient safety data. Clinical evidence suggests that the time to achieve amyloid plaque clearance (defined as <24.1 Centiloids) varies with baseline amyloid levels, with greater baseline burden correlating with higher likelihood of clearance [15].

FDA Approval & Therapeutic Insights: Donanemab-azbt, commercially known as Kisunla™, received U.S. Food and Drug Administration (FDA) approval on July 2, 2024 for the treatment of early symptomatic Alzheimer's disease, including adults with mild cognitive impairment (MCI) and those in the mild dementia stage of Alzheimer's disease with confirmed amyloid pathology. Kisunla is distinguished from earlier amyloid-targeting therapies by its limited-duration treatment regimen: it is the first approved plaque-targeting antibody that allows stopping treatment once amyloid plaques are reduced to minimal levels, as confirmed by amyloid PET imaging. This approach can lower the number of infusions and overall treatment burden compared with continuous dosing strategies [16].

Donanemab Approval in India: Donanemab, marketed for early Alzheimer's disease, was approved in India by the Central Drugs Standard Control Organization (CDSCO) Donanemab's regulatory clearance in India follows earlier approvals in the United States, Japan, and China, and underscores its emerging role as one of the first disease-modifying treatments available in multiple international markets. The therapy is administered as monthly injections andrepresents an important advance in dementia care, particularly as demand for effective Alzheimer's interventions continues to grow with rising prevalence [17].

5.2.3. Analytical methods of donanemab

- ELISA- Enzyme linked immuno sorbate assay
- ELISA-Based Analytical Approaches in the Donanemab

ELISA-based immunoassays were used to quantify circulating biomarkers associated with Alzheimer's disease pathology, particularly soluble amyloid-β (Aβ) peptides and tau-related markers in plasma and cerebrospinal fluid (CSF). These assays enabled sensitive measurement of changes in Aβ species following donanemab administration, providing biochemical evidence of target engagement that complemented florbetapir F-18 PET imaging. The observed reductions in amyloid plaque burden were supported by immunoassay data demonstrating alterations in amyloid-related biomarkers consistent with accelerated plaque clearance.

In addition, ligand-binding immunoassays, commonly developed in ELISA or electrochemiluminescence formats, were used for pharmacokinetic assessment of donanemab, allowing characterization of systemic exposure, dose proportionality, and temporal drug concentration profiles. Such assays are essential for monoclonal antibody development, as they provide robust quantification of therapeutic antibodies in biological matrices and support exposure–response analyses.

The integration of ELISA-based biomarker measurements played a critical supportive role in confirming the biological activity of donanemab and in linking amyloid removal to downstream biochemical changes. These immunoassay approaches remain central to donanemab's clinical development, serving as scalable and validated tools for biomarker monitoring in large Alzheimer's disease trials [18].

Donanemab was evaluated for its clinical efficacy and safety in patients with early symptomatic Alzheimer's disease. While the primary endpoints focused on cognitive and functional outcomes and amyloid plaque reduction assessed by PET imaging, ELISA-based immunoassays constituted an important component of the trial's bioanalytical and biomarker evaluation strategy.

ELISA and related ligand-binding immunoassays were used to support pharmacokinetic (PK) analyses of donanemab, enabling the quantification of circulating drug concentrations in serum or plasma across treatment intervals. These assays provided essential data on systemic exposure, dose consistency, and temporal pharmacokinetic profiles, which are critical for confirming appropriate target engagement and informing dose–response relationships in large-scale clinical trials involving monoclonal antibodies. These immunoassay-derived biomarker data complemented amyloid PET findings, supporting the mechanistic link between amyloid removal and attenuation of disease-related biochemical pathways.

ELISA techniques were also integral to immunogenicity assessment, specifically for the detection of anti-donanemab antibodies. Monitoring immunogenic responses is particularly important in long-term monoclonal antibody therapy, as anti-drug antibodies may influence pharmacokinetics, efficacy, or safety outcomes. Although immunogenicity findings were not a primary focus of the JAMA report, ELISA-based assays remain the standard platform for such analyses in regulatory-compliant clinical trial.

ELISA-based immunoassays functions as robust, scalable tools for drug quantification, biomarker monitoring, and immunogenicity evaluation, complementing imaging biomarkers and clinical endpoints. These approaches reinforced the biological plausibility of donanemab's clinical effects and supported its characterization as a disease-modifying therapy in early Alzheimer's disease [19].

Sandwich ELISA assays are commonly employed to measure serum or plasma concentrations of donanemab in preclinical and clinical studies. These assays typically use a capture antibody directed against the Fc or variable region of donanemab, combined with a detection antibody recognizing a distinct epitope, enabling selective quantification in complex biological matrices [20].

5.3. Mass spectroscopy

Mass spectrometry has been widely applied in Alzheimer's disease research for the discovery and validation of amyloid-β and tau biomarkers. The use of targeted LC–MS/MS approaches to quantify amyloid peptides and disease-relevant protein modifications, providing a methodological foundation for evaluating pharmacodynamic responses to anti-amyloid therapies such as donanemab, although the antibody itself was not directly quantified by mass spectrometry [21].

Mass spectrometry has been extensively used to quantify site-specific tau phosphorylation and turnover in Alzheimer's disease. Targeted LC–MS/MS is used to demonstrate differential tau phosphorylation kinetics between brain and CSF compartments. Although donanemab was not directly measured, such MS-based tau analyses provide sensitive pharmacodynamic biomarkers to assess downstream biological effects of anti-amyloid therapies such as donanemab [22].

Mass-spectrometry–based immuno-epitope mapping has been used to characterize donanemab's binding specificity. Applied immuno-affinity enrichment coupled with LC–MS/MS is used to identify aggregation-dependent Aβ sequence and modification fingerprints, demonstrating selective recognition of pyroglutamate-modified Aβ3-x species by donanemab. This approach provides mechanistic insight into antibody specificity but is not intended for pharmacokinetic quantification [23].

5.4. Role of Targeted Mass Spectrometry in Donanemab Evaluation

Targeted mass spectrometry (TMS) is employed to precisely quantify Alzheimer's disease (AD) biomarkers in cerebrospinal fluid (CSF) and blood, including amyloid-β (Aβ) peptides and tau proteins, which are central to AD pathology. TMS methods such as selected reaction monitoring (SRM) and parallel reaction monitoring (PRM) allow specific measurement of pre-selected peptides with high analytical specificity and reproducibility, complementing traditional immunoassays by providing detailed molecular characterization of both full-length and proteolytically processed forms of amyloid and tau proteins. This method doesn't directly measure therapeutic antibodies like donanemab, but the biomarkers quantified by TMS — particularly the Aβ42/Aβ40 ratio and other amyloid-related peptide signatures — are key pharmacodynamic endpoints in clinical trials of amyloid-targeting therapies. Quantitative MS can therefore support assessment of donanemab's biochemical effects by enabling sensitive tracking of changes in amyloid species in biological fluids, which may reflect drug-induced amyloid clearance. Because TMS can distinguish specific peptide variants and post-translational modifications, it provides a powerful tool for validating and refining biomarker panels used to monitor disease progression and treatment response in trials of donanemab and similar agents [24].

5.5. Mass Spectrometry–Based Amyloid Analysis and Relevance to Donanemab Therapy

The multiplex liquid chromatography–mass spectrometry (LC–MS)–based approach is used for the quantitative analysis of endogenous amyloid-β (Aβ) peptides in human plasma, including Aβ38, Aβ40, Aβ42, and APP669–711. This approach does not directly analyze donanemab or other therapeutic monoclonal antibodies, but it provides a robust analytical framework for monitoring amyloid dynamics relevant to anti-amyloid therapies such as donanemab. This approach demonstrate that MS-based measurement of plasma Aβ42/Aβ40 ratios strongly correlates with cerebral amyloid burden assessed by PET imaging, highlighting its potential utility as a pharmacodynamic biomarker. Such high-precision mass spectrometry assays are increasingly important in donanemab clinical development, as they enable objective assessment of amyloid clearance, treatment response, and disease modification without reliance solely on neuroimaging. Consequently, MS-based plasma amyloid profiling represents a complementary tool for evaluating the biochemical impact of donanemab and other disease-modifying therapies in Alzheimer's disease [25].

Figure 5 Mass Spectrometer

5.6. LC–MS-Based Bioanalytical Strategies Relevant to Donanemab Characterization

Liquid chromatography–mass spectrometry (LC–MS) has become a cornerstone analytical platform for the characterization and quantification of complex biotherapeutics. The current LC–MS-based strategies used for antibody-drug conjugates (ADCs), many of which are directly applicable to monoclonal antibodies such as donanemab. These strategies include bottom-up peptide mapping, middle-down subunit analysis, and intact protein mass spectrometry, enabling detailed evaluation of molecular integrity, sequence confirmation, and post-translational modifications. Although donanemab is not an ADC, similar LC–MS workflows can be employed to characterize its structural heterogeneity, monitor degradation or modification, and ensure batch-to-batch consistency during development and clinical use.

In the context of donanemab bioanalysis, LC–MS methods—often combined with immunoaffinity enrichment—enable sensitive and selective quantification of the therapeutic antibody in complex biological matrices such as plasma or serum. Targeted LC–MS assays using signature peptides derived from the antibody's variable regions allow accurate measurement of drug concentrations for pharmacokinetic and exposure–response studies, complementing conventional ligand-binding assays. Furthermore, LC–MS offers superior molecular specificity, enabling differentiation between intact drug, modified forms, and potential degradation products that may influence efficacy or immunogenicity. The LC–MS-based analytical strategies provide a robust framework for the comprehensive characterization and quantification of therapeutic antibodies, supporting the pharmacological evaluation and clinical development of anti-amyloid agents such as donanemab [26].

5.7. Mass Spectrometry–Based Tau Quantification and Its Relevance to Donanemab Evaluation

Targeted immunoprecipitation mass spectrometry (IP-MS) approach is employed to simultaneously quantify multiple plasma tau species, including six phosphorylated forms (p-tau181, p-tau199, p-tau202, p-tau205, p-tau217, p-tau231) and two non-phosphorylated tau peptides, in a cohort of participants spanning the Alzheimer's disease (AD) continuum. This methodological framework enables the precise measurement of distinct tau fragments in blood with high analytical specificity, overcoming limitations of immunoassays that depend on epitope availability. The study demonstrated that particular phosphorylated tau variants, notably p-tau217, p-tau231, and p-tau205, show differential associations with amyloid plaque burden and tau pathology determined by PET imaging, making them highly informative biomarkers of AD pathology and progression.

Although this method did not directly analyze donanemab or other therapeutic monoclonal antibodies, the MS-based quantification of tau species described is directly relevant to clinical trials of anti-amyloid agents like donanemab. In trials of donanemab, changes in plasma biomarkers such as phosphorylated tau species are increasingly used as pharmacodynamic endpoints to monitor treatment response, correlate biochemical effects with amyloid clearance, and understand downstream effects on tau pathology. The ability of targeted MS to differentiate multiple tau proteoforms and link them with underlying amyloid and tau pathologies provides a powerful analytical tool for assessing how

donanemab influences disease biology beyond amyloid reduction, particularly in studies assessing disease progression and staging [27].

Targeted high-resolution mass spectrometry (MS) approach is employed to generate differential tau protein profiles in cerebrospinal fluid (CSF) from patients with Alzheimer's disease (AD), progressive supranuclear palsy, and dementia with Lewy bodies. Using an innovative pre-fractionation strategy and multiplex peptide detection, the authors quantified tau-specific peptides spanning the entire sequence of the protein, overcoming the limitations of immunodetection methods that are constrained by antibody specificity and affinity. The MS results revealed that while core tau profiles were similar across tauopathies, AD was distinguished by a unique distribution of peptide species and post-translational modifications, reflecting the complex heterogeneity of tau proteoforms in pathological states [28].

Figure 6 Mass Spectroscopy

6. Conclusion

Alzheimer's disease (AD) is a multifactorial and progressive neurodegenerative disorder, resulting from the interplay of multiple pathogenic mechanisms, including extracellular amyloid-β (Aβ) plaque deposition, intracellular tau hyperphosphorylation leading to neurofibrillary tangles, chronic neuroinflammation, synaptic loss, and metabolic dysfunction within neurons. Collectively, these processes contribute to progressive cognitive decline, memory impairment, and loss of functional independence in affected individuals. While understanding of the molecular and genetic underpinnings of AD has significantly advanced—highlighting key risk factors such as mutations in APP, PSEN1, PSEN2, and the APOE ε4 allele—current treatment options remain primarily symptomatic, addressing only neurotransmitter deficits without modifying the underlying disease progression.

The emergence of anti-amyloid immunotherapies, particularly monoclonal antibodies like donanemab, represents a pivotal advancement in the development of disease-modifying interventions. Donanemab specifically targets pyroglutamate-modified Aβ, facilitating amyloid plaque clearance in early-stage AD, and has demonstrated measurable reductions in amyloid burden along with modest slowing of cognitive decline. However, its use necessitates careful monitoring for amyloid-related imaging abnormalities (ARIA), emphasizing the importance of balancing efficacy with safety.

Complementary analytical and biomarker-driven approaches have been instrumental in advancing therapeutic evaluation. Techniques such as ELISA-based immunoassays, targeted mass spectrometry, cerebrospinal fluid (CSF) biomarker quantification, plasma biomarker analysis, and advanced neuroimaging modalities (including PET scans) enable precise monitoring of disease progression, treatment response, and pharmacokinetics. These tools enhance mechanistic understanding, facilitate early detection, and support precision medicine strategies tailored to individual patients.

In summary, continued research integrating molecular insights, innovative bioanalytical methods, multi-modal imaging, and long-term clinical assessment is essential to optimize therapeutic strategies, improve patient outcomes, and advance the management of Alzheimer's disease toward effective disease-modifying solutions.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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