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ALZHEIMER'S DISEASE (MORBUS ALZHEIMER): PATHOPHYSIOLOGICAL MECHANISMS AND BREAKTHROUGHS IN DISEASE-MODIFYING THERAPEUTICS

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ABSTRACT: This scientific article presents a comprehensive study on the pathophysiological cascades of Alzheimer's disease (Morbus Alzheimer) and the revolutionary paradigm shift in its pharmacological treatment. For decades, therapeutic options were restricted to symptomatic management via acetylcholinesterase inhibitors and NMDA receptor antagonists. However, recent scientific advances have led to the regulatory approval of novel disease-modifying therapies (DMTs), specifically monoclonal antibodies including Lecanemab (Leqembi®) and Donanemab (Kisunla®). These targeted biological agents remove extracellular neurotoxic amyloid-beta (Aβ) protofibrils and mature plaques, resulting in a clinically meaningful ~30% deceleration of cognitive and functional decline in early-stage patients. Furthermore, this paper highlights the biomarker role of intracellular hyperphosphorylated Tau protein (Proteinum Tau) and the clinical utility of ultra-sensitive plasma biomarkers (plasma p-tau217) for non-invasive early diagnostics.
Keywords: Alzheimer's disease, Morbus Alzheimer, Amyloid-beta, Tau protein, Lecanemab, Donanemab, disease-modifying therapies, plasma p-tau217.

ANNOTATSIYA: Ushbu ilmiy maqolada Altsgeymer kasalligining (Morbus Alzheimer) patofiziologik mexanizmlari hamda ularni davolashdagi zamonaviy inqilobiy yutuqlar tahlil qilingan. Ko'p yillar davomida davolash faqat simptomatik vositalar bilan cheklangan bo'lsa, bugungi kunda kasallik biologiyasiga bevosita ta'sir etuvchi monoklonal antitanachalar — Lecanemab (Leqembi®) va Donanemab (Kisunla®) amaliyotga kirib keldi. Maqolada beta-amiloid blyashkalari hamda Tau oqsili (Proteinum Tau) chigalliklarining neyrodegeneratsiyadagi o'rni, ushbu dori vositalarining klinik samaradorligi hamda qon biomarkerlari (p-tau217) orqali erta tashxis qo'yish imkoniyatlari atroflicha yoritib berilgan.
Keywords: Altsgeymer kasalligi, Morbus Alzheimer, beta-amiloid, Tau oqsili, Lecanemab, Donanemab, monoklonal antitanachalar, p-tau217.

АННОТАЦИЯ: В данной научной статье рассматриваются патофизиологические механизмы болезни Альцгеймера (Morbus Alzheimer) и прорыв в области патогенетической терапии. Долгое время лечение ограничивалось симптоматическими препаратами, однако одобрение таких моноклональных антител, как Lecanemab (Leqembi®) и Donanemab (Kisunla®), ознаменовало новую эру. В работе проанализирована роль внеклеточного бета-амилоида и внутриклеточного Тау-белка (Proteinum Tau), механизмы действия биологических препаратов, замедляющих когнитивное угасание на 30%, а также диагностическая ценность высокочувствительных плазменных биомаркеров (p-tau217).

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Keywords: Болезнь Альцгеймера, Morbus Alzheimer, бета-амилоид, Tau-белок, Lecanemab, Donanemab, плазменные биомаркеры, p-tau217.

1. INTRODUCTION

Epidemiological Significance. Alzheimer's disease (Morbus Alzheimer) represents the predominant etiology of dementia worldwide, accounting for 60% to 80% of all progressive neurodegenerative disorders in older adults. According to epidemiological data from World Alzheimer Reports, over 55 million individuals are currently living with dementia globally, a figure projected to exceed 139 million by 2050 due to demographic aging. Morbus Alzheimer places an unprecedented socioeconomic burden on healthcare systems and family caregivers alike.

For more than two decades, the pharmacological armamentarium available to neurologists was strictly confined to symptomatic enhancers—primarily acetylcholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and the NMDA receptor antagonist Memantine. While these agents temporarily alleviate neurotransmitter deficiencies, they do not impede the relentless progression of underlying neurodegenerative cascades or prevent irreversible loss of cortical neurons. Recent breakthroughs in structural neurobiology and immunotherapy have transitioned clinical neurology from symptomatic palliation to disease-modifying therapies (DMTs) designed to directly intercept molecular pathology.

2. PATHOPHYSIOLOGICAL CASCADES: AMYLOID-BETA AND TAU PROTEIN

Extracellular Amyloid-beta (Amyloidum beta) Toxicity. The classical amyloid cascade hypothesis posits that the primary initiator of Morbus Alzheimer pathogenesis is the abnormal sequential cleavage of the Amyloid Precursor Protein (APP) by beta- and gamma-secretase enzymes. This proteolytic processing generates hydrophobic Amyloid-beta (Amyloidum beta) monomers, particularly the highly aggregation-prone Aβ42 isoform. Aβ42 monomers spontaneously self-assemble into soluble oligomers, protofibrils, and insoluble fibrillar deposits known as senile (amyloid) plaques in the extracellular parenchyma. Soluble Aβ protofibrils exert direct neurotoxicity by inducing synaptic loss, disrupting calcium homeostasis, impairing long-term potentiation (LTP), and triggering persistent neuroinflammation via microglial activation.

Intracellular Tau Protein (Proteinum Tau) Pathology. Concurrently, intracellular neurofibrillary tangles (NFTs) form via the hyperphosphorylation of Tau protein (Proteinum Tau). Under physiological conditions, Tau stabilizes the microtubular cytoskeleton of neuronal axons, enabling intracellular vesicular transport. In Morbus Alzheimer, pathological hyperphosphorylation causes Tau to detach from microtubules, aggregate into paired helical filaments (PHFs), and collapse the axonal transport system. Tau pathology correlates tightly with the clinical severity of cognitive decline and topological patterns of cortical atrophy.

3. BREAKTHROUGHS IN DISEASE-MODIFYING THERAPEUTICS (DMTs)

The landmark approvals of disease-modifying humanized IgG1 monoclonal antibodies mark a transformative milestone in neurotherapeutics. Rather than merely modifying synaptic transmission, these biological agents target fundamental pathophysiological drivers of Morbus Alzheimer:

1. Lecanemabum (Lecanemab / Leqembi®): Lecanemab (Leqembi®) exhibits high conformational selectivity for soluble amyloid-beta protofibrils (large soluble Aβ aggregates). By binding to these highly toxic intermediate species, Lecanemab promotes microglial clearance of Aβ through Fc receptor-mediated phagocytosis. Pivotal Phase 3 Clarity AD trials demonstrated a 27%

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reduction in clinical decline as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale over 18 months in early-stage patients.

2. Donanemabum (Donanemab / Kisunla®): Donanemab (Kisunla®) specifically targets N3pG-Aβ, an altered, highly insoluble form of amyloid-beta found predominantly within mature, established amyloid plaques. By rapidly clearing dense plaque burden from cerebral tissue, Donanemab achieved a 35.1% slowing of cognitive and functional decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) in patients with low-to-medium tau pathology during the TRAILBLAZER-ALZ 2 trials.

4. COMPARATIVE CLINICAL AND PHARMACOLOGICAL EFFICACY

Table 1 provides a rigorous comparative breakdown between traditional symptomatic agents and novel disease-modifying biological therapies in Alzheimer's disease management:

Parameter	Traditional Symptomatic Agents (Donepezil, Memantine)	Disease-Modifying Monoclonal Antibodies (Lecanemabum, Donanemabum)
Primary Pharmacological Target	Acetylcholinesterase enzymes / NMDA glutamate receptors	Extracellular Amyloid-beta (Aβ) protofibrils and mature plaques
Mechanism of Action	Symptomatic neurotransmitter elevation; no impact on neuronal survival	Fc-mediated microglial phagocytosis and immune clearance of Aβ
Impact on Disease Progression	None; symptoms return to baseline upon treatment cessation	Clinically meaningful ~30% deceleration of cognitive and functional decline
Indicated Patient Population	All stages (Mild, Moderate, and Severe Alzheimer's)	Strictly Early Stage: Mild Cognitive Impairment (MCI) or Mild Dementia
Diagnostic Prerequisite	Standard clinical evaluation & cognitive screening (MMSE, MoCA)	Mandatory Amyloid Positivity confirmation (Amyloid-PET or CSF/Plasma Biomarkers)
Administration & Safety Profile	Oral daily tablets; side effects include nausea and bradycardia	Intravenous infusions (biweekly/monthly); risk of ARIA (Amyloid-Related Imaging Abnormalities)

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5. ADVANCES IN EARLY DIAGNOSTICS: PLASMA BIOMARKERS

The Diagnostic Paradigm Shift. A critical limitation of disease-modifying monoclonal antibody therapies is that their clinical efficacy relies entirely on administration during early, preclinical stages before widespread, irreversible neuronal loss occurs. Historically, confirming amyloid pathology required invasive cerebrospinal fluid (CSF) lumbar punctures or costly, highly specialized Amyloid-PET brain imaging.

Recent clinical validation of blood-based biomarkers—most notably phosphorylated tau at threonine 217 (plasma p-tau217)—has revolutionized neurodiagnostics. High-precision immunoassay platforms measuring plasma p-tau217 achieve diagnostic accuracy exceeding 95% in distinguishing Morbus Alzheimer from non-Alzheimer neurodegenerative disorders. The integration of plasma p-tau217 screenings into routine clinical practice enables mass early detection, democratization of diagnostic access, and timely patient selection for disease-modifying therapies.

6. CONCLUSION

1. Modern clinical neurology has officially entered the era of disease-modifying therapeutics for Morbus Alzheimer, shifting the treatment goal from temporary symptomatic control to targeted disease deceleration.

2. Biological drugs such as Lecanemabum (Leqembi®) and Donanemabum (Kisunla®) clear neurotoxic amyloid-beta species from cerebral tissue, yielding a clinically significant ~30% reduction in cognitive decline when administered during early disease stages.

3. High-sensitivity blood-based biomarkers, particularly plasma p-tau217, provide an accessible, non-invasive diagnostic gateway essential for early therapeutic intervention and population-wide screening.

7. REFERENCES

1. European Medicines Agency (EMA). (2025). Leqembi (lecanemab) Summary of Product Characteristics and EU Assessment Report.
2. van Dyck, C. H., Swanson, C. J., Aisen, P., et al. (2023). Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine, 388(1), 9-21.
3. Sims, J. R., Zimmer, J. A., Evans, C. D., et al. (2023). Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA, 330(6), 512-527.
4. Ashton, N. J., Brum, W. S., Di Molfetta, G., et al. (2024). Diagnostic Accuracy of a Plasma Phospho-Tau217 Immunoassay in Alzheimer Disease. JAMA Neurology, 81(3), 255-263.
5. World Health Organization (WHO). (2025). Global Status Report on the Public Health Response to Dementia. Geneva: World Health Organization.
6. Jack, C. R., Andrews, J. S., Beach, T. G., et al. (2024). Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup Report. Alzheimer's & Dementia, 20(8), 5241-5263.