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Role of Dasatinb in Alzheimer's Disease: Review Article

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease (NDD) characterized by dementia among old age subjects**.** In spite of the intense and persistent effects of AD, currently available therapeutic modalities demonstrated unsatisfactory results and couldn't stop disease progression**.** Dasatinib is a tyrosine kinase (TK) inhibitor (TKI) that has immunomodulatory characteristics and could cross the blood-brain barrier (BBB). It's an FDA-approved drug utilized to treat resistant lymphoblastic or chronic myeloid leukemia (CML) in those who didn't respond to preceding therapies.

Objectives: This literature was conducted to assess the role of dasatinib an AD.

Methods: Data were collected from online review articles and papers from the PubMed, Science direct and Google scholar. We searched for Alzheimer's disease, Dasatinib, Dementia and Tyrosine kinase. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 2006 to 2024 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: Dasatinib appears to be a talented therapy of AD. Dasatinib not only attenuate amyloid and tau proteins, which are the main feature of AD pathology, but also has very important immune-modulatory function as it decreases pro-inflammatory markers and increasing anti-inflammatory cytokines (i.e. IL-10). Furthermore, dasatinib decreases activated microglia, and acts as a senolytic drug decreasing senescent cells (SnCs) in brain.

Keywords: Alzheimer's disease, Dasatinib, Dementia, Tyrosine kinase.

INTRODUCTION

Alzheimer's disease (AD):

Alzheimer's disease (AD) is a progressive NDD characterized by dementia among old age subjects [1]. Genetic and environmental predisposing factors have a main role in the etiology of AD development. Of note, age has been considered the main predisposing factor for AD development [2].

Regarding AD types, it could be classified according to time of occurrence into two main types: Early-onset AD (before the age of sixty-five) and late-onset AD (over sixty-five years of age), and it represents the majority of the affected subjects (95%) of cases [3].

Neuritic plaques and neurofibrillary tangles (NFTs), two main definitive features among cases of AD. They occur due to amyloid-beta (Aβ) deposition and tau aggregation and usually affect the medial temporal lobe and neocortex [4].

Pathology starts within the hippocampal and entorhinal areas and then all over both the frontal and temporal areas. It frequently spares the cerebellum and extends as far as the striatum and thalamus [5].

Amyloid-beta (Aβ) plaques:

Amyloid-beta a protein consisting of 37–49 amino acids, the primary component of the amyloid plaques, which are resistant to degradation [6]. They frequently localise with neuronal debris and stimulated microglia and astrocytes [7]. Numerous studies displayed a strong relationship between Aβ deposition and both impaired cognitive functions and dementia degree [8].

Neuronal fibrillary tau tangles (NFTs):

Tau protein is microtubules associated protein. It's involved in microtubule assembly and stabilization [9]. The affinity of tau to tubulin is modified by different post-translational modifications such as phosphorylation, acetylation, methylation, oxidation, and ubiquitination. Among these post-translational modifications widely evaluated, the most notable are tau phosphorylation and acetylation [10].

It has been demonstrated that the PTM of tau protein is the main mechanism across which tau aggregation and neurodegeneration happened [11]. Abnormalities in phosphorylated tau protein have been demonstrated to be associated with dissociation of tau protein from microtubules, with a subsequent reduction in microtubule stability and promotion of microtubule depolymerization. Hyperphosphorylation predisposes tau filaments to coalesce into NFTs [12].

Also, acetylation of tau renders it insoluble by neutralizing the repulsive action of positively charged lysine residues, encouraging tau aggregation, and suppressing tau degradation [13]. Tau accumulation causes synaptic dysfunction, inflammation, and impaired mitochondrial functions, eventually causing neurodegenerative changes [14].

Cholinergic hypothesis:

One of the first neurons in the basal forebrain to be affected by AD is cholinergic neurons, and the transcription and activity of choline acetyltransferase in the remaining neurons are decreased [15]. In addition,

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these neurons have main roles in learning and memory, as well as cognitive functions [16].

Of note, nicotinic receptors are abundant in the hippocampus [17]. The major etiology of memory affection is believed to be due to synaptic dysfunction between the target tissues of the hippocampal and cerebral areas and the basal forebrain, which results in the grad of dementia [18, 19].

Mitochondrial dysfunction and oxidative stress:

Changes in mitochondrial structure, numbers, and transfer, diminished cytochrome oxidase activities, deficits in metabolic proteins, alterations in mitochondrial membrane potential, and the release of free radicals are all noticed in AD. Neurons are in particular sensitive as they cannot divide and could not be substituted throughout the damaging process, causing impaired mitochondrial function in the future [20].

Inflammation:

The innate immune cells comprised in the neuroinflammation process are mainly microglia and astrocytes, whereas capillary endothelial cells and infiltrating blood cells also may play a role, especially when there's damage in the BBB. When BBB is disrupted, toxic blood proteins could pass to the brain, with subsequent alteration of the internal environment.

The process is characterized by the formation of pro-inflammatory cytokines including IL-1β, IL-6, TNF, chemokines, and the release of free radicals by microglia [21]. Of note, the formation of pro-inflammatory mediators is always associated with impaired synapse function, neuronal death, and suppression of neurogenesis [22].

Dasatinib:

Dasatinib is an oral 2nd-generation multikinase inhibitor (MKI). Dasatinib is used to treat cases with Philadelphia chromosome-positive (Ph^+) CML and Ph^+ acute lymphoblastic leukemia (ALL) who give no response to imatinib. In addition, it has become the drug of choice in the context of CML treatment. Dasatinib is MKI targeting BCR-ABL, the SRC family kinases (SFKs) and receptor TK (RTKs) [23].

Inhibition of BCR-ABL:

The BCR-ABL gene causes deregulation of kinase activities, which encourages growth and replication, causing impairment of apoptosis (programmed single cell death) and uncontrolled proliferation. The constitutively active ABL TK is an active driver in CML and in Ph+ ALL. The suppression of BCR-ABL TK activity has been demonstrated to be associated with the apoptotic induction and inhibition of cellular proliferation [24].

Inhibition of SRC family kinases (SFKs):

Dasatinib is an inhibitor of SFKs (A class of structurally-related non-RTKs). SFKs are comprised in complex signal transduction. By inhibiting SRC, dasatinib could block the process of cellular duplication, and invasion, and it stimulates apoptosis of cancer cells. In addition, it reduces the risk of metastases and acts on the tumor microenvironment [23].

Inhibition of receptor tyrosine kinases (RTKs):

Dasatinib suppresses a lot of RTKs, such as the c-KIT receptor TK comprised in proliferation, differentiation, and cellular survival. Activating mutations of c-KIT are accompanied by various human tumours, comprising most cases with systemic mast cell disorders [25].

Dasatinib as a senolytic drug:

Senescent cells (SnCs) are characterized by permanent cell-cycle arrest and are resistant to apoptosis and often increase the rate of metabolic activities [26].

The burden of SnCs increases with advanced age and NDDs, and happens through cell types comprising neurons, microglia, astrocytes, and endothelial cells [27].

In addition, SnCs may develop a distinctive pathogenic SASP that releases a broad range of bioactive factors, such as inflammatory cytokines, chemokines, growth factors, lipids, nucleotides, extracellular vesicles, and soluble factors, which in turn drive secondary senescence and disturb normal tissue homeostasis, which ultimately ends in the affection of tissue repairing and regenerating mechanisms [28].

Using gene expression in cadaveric cerebral tissue from subjects with AD; it was demonstrated that neurons with NFTs include profiles matched with SnCs. These involve upregulation of pro-survival and downregulation of cell death pathways [29]

It has been demonstrated that SnCs are accompanied by tau deposition. SnC clearance decreases neurodegenerative changes, cerebral atrophy, enlarged ventricles, and impaired cognition. As a result, tau-related SnCs could be considered a promising new target for intervention [28].

Senolytic drugs are medications that clear SnCs in a selective manner and include Dasatinib, Quercetin, and Navitoclax [26].

Dasatinib acts by transiently disabling the SnC anti-apoptotic pathways that defend SnCs from apoptosis, causing apoptosis of SnCs together with the tissue-damaging SASP [30].

Promising effects of dasatinb demonstrated by different AD animal models:

Recent studies used dasatinib on different Alzheimer disease animal models either alone or in combination with quercetin (a natural plant-derived flavonoid). A study conducted by **Fang *et al.*** [31] who used dasatinib plus quercetin on AD mice model; $APP^{NL-F/NL-F}$ mice, which demonstrate elevated Aβ protein due to APP overexpression and demonstrated that combined dasatinib and quercetin in female $APP^{NL-F/NL-F}$ mice diminished SASP markers in plasma,

and hippocampus. In addition, combined dasatinib and quercetin in female $APP^{NL-F/NL-F}$ mice diminished hippocampal $A\beta_{42}$.

The combination of these elements improved females' spatial learning and memory in $APP^{NL-F/NL-F}$ mice. Dasatinib plus quercetin were also found to reduce microgliosis and ameliorate both Aβ and tau pathology in 3xTg mice (expressing three mutations; human APP, tau and Psen1) **[32].**

Moreover, dasatinib has a beneficial effect in modulating neuronal inflammation as demonstrated in the study by **Dhawan and Combs [33]** who found that dasatinib not only decreased protein phosphotyrosine, reactive microglia but also decreased pro-inflammatory mediator (TNFα level in the hippocampus and temporal cortex of dasatinib treated mice).

Using the same animal model (mice), **Zhang *et al.* [28]** demonstrated that the concentrations of the pro-inflammatory IL-1β was significantly diminished in the brain of dasatinib plus quercetin-managed AD mice compared to the control group.

In addition to its role in reducing pro-inflammatory markers, dasatinib also mediates the release of anti-inflammatory cytokines such as IL-10, through the induction of regulatory-like macrophages at the inflammatory areas **[34]**.

CONCLUSION

Dasatinib appears to be a talented therapy for AD. This may need further studies to be demonstrated, but overall it has many beneficial effects on the disease pathology. Dasatinib not only attenuates amyloid and tau proteins, the main feature of AD pathology, but also has a very important immune-modulatory function, as it decreases pro-inflammatory markers (TNF-α and IL-1 beta) and increases anti-inflammatory cytokines (i.e., IL-10). Furthermore, dasatinib decreases activated microglia and acts as a senolytic drug, decreasing senescent cells in the brain.

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