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Drug Development in Alzheimer's Disease

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Abstract
Alzheimer's is one of the most common forms of dementia, this pathological condition is mostly experienced by older people (especially age> 85 years). Dementia is an acquired, persistent, and progressive intellectual failure, and is accompanied by memory loss and at least one cognitive symptom. One of the cognitive symptoms is aphasia (word finding difficulty), apraxia (inability to perform motor task), agnosia (inability to recognize object), and impaired executive function (poor abstraction, mental flexibility, planning, and judgment). Based on histochemical/ microscopic examination can be found neuritic plaque and neurofibrillary tangles. On the cerebrospinal fluid examination, Aβ42 levels can be found low and increased levels of protein tau. Multiple neurotransmitter abnormalities also contribute to the development of Alzheimer's disease, particularly cholinergic transmission failure. In addition, other neurotransmitter abnormalities such as glutamate, serotonin and substance P are also seen. Treatment for Alzheimer's disease to date is limited to cognitive symptoms, there is no treatment aimed at treating (curative) or overcoming the major problems that cause Alzheimer's (amelioration). Many potential new therapeutic / pharmacologic agents, still in the process of research / investigation to date. Alzheimer's Association International Conference (AAIC), the researchers reported that the β-secretase inhibitor drug could significantly decrease Aβ levels in mild-moderate Alzheimer's. Verubecestat is a class of β-secretase inhibitor (BACE1 inhibitor) drugs that enter in phase 3 clinical trial.

Keyword: *alzheimer 's disease, Verubecestat, B-Secretase Inhibitor.*

I. INTRODUCTION

The brain consists of 4 parts of the cerebrum, disensefalon, brain stem, and cerebellum. The cerebrum or cerebrum is the largest part of the brain, about 85% of the brain is a cerebrum. Serebrum plays a role in processing somatic sensory stimuli, motor information, awareness, and intellectual/ cognitive functions (Marieb and Hoehn, 2013). In the transmission of signals between neurons can involve multiple neurotransmitters, there was more than 50 chemical substances are expressed as neurotransmitters, which are grouped into 2 ie fast-acting small molecule neurotransmitters and large slow-working molecular neurotransmitters. One of the fast-acting molecular neurotransmitters are acetylcholine, norepinephrine, epinephrine, glutamate, glycine etc (Hall, 2016). Acetylcholine has a function associated with the contractility of the skeletal muscle and the regulation of heart rate, neurotransmitters are also found in different regions of the brain. Based on the latest information acetylcholine in the brain have a role in memory, attention, intellectual, and sleep (Miller, et al., 2008). Alzheimer's is one of the most common forms of dementia, this pathological condition is mostly experienced by older people (especially age> 85 years). Dementia is an acquired, persistent, and progressive intellectual failure, and is accompanied by memory loss and at least one cognitive symptom. One of the cognitive symptoms is aphasia (word finding difficulty), apraxia (inability to perform motor task), agnosia (inability to recognize object), and impaired executive function (poor abstraction, mental flexibility, planning, and judgment) (Harper, Johnston, and Landefeld, 2016). Approximately 5.4 million Americans suffer from Alzheimer's (Winslow, et al., 2011), while dementia data in the UK in 2010 amounted to 700 thousand. The 2009 Alzheimer's disease international (ADI) estimates that in 2010 the total number of dementia sufferers worldwide was 36 million, and by 2050 it grew to 115 million. Increased longer life expectancy, followed by an increase in the prevalence of dementia because of the close correlation between the two (Hughes, 2011). Alzheimer's disease is included in the top 10 diseases that often cause death in America (Pignone and Salazar, 2016).

II. ETHIOLOGY & CLINICAL MANIFESTATION OF DEMENTIA

The cause of dementia is highly variable, including degenerative diseases, intoxication, vascular abnormalities in the brain, trauma, infections, and metabolic abnormalities (Sharpe and Lawrie, 2014). Etiology or causes of dementia do vary but Alzheimer's disease and vascular disease are the most common cause of dementia. Several other types of dementia such as lewy body dementia and fronto-temporal dementia also occur despite lesser prevalence. There are differences in different types of dementia both in terms of clinical manifestations and their pathological appearance. Alzheimer's disease generally occurs in elderly patients who have decreased memory slowly and progressively in a few years, generally not affecting the motor. Fronto-temporal dementia is characterized by changes in personality, increased obesession and interest in mainly fatty foods, progressive aphasia, and apathy. lewy body dementia is usually characterized by the appearance of visual hallucinations, parkinsonism, and sleep disorder (Sharpe and Lawrie, 2014; Aminoff and Kerchner, 2016). Table 1 shown common cuase of dementia.

Table 1. Common Cause of Dementia (Aminoff and Kerchner, 2016).

Disorder	Pathology	Clinical Features
Alzheimer disease	Plaques containing beta-amyloid peptide, and neurofibrillary tangles containing tau protein, occur throughout the neocortex	• Most common age-related neurodegenerative disease; incidence doubles every 5 years after age 60 • Short-term memory impairment is early and prominent in most cases • Variable deficits of executive function, visuospatial function, and language
Vascular dementia	Multifocal ischemic change	• Stepwise or progressive accumulation of cognitive deficits in association with repeated strokes • Symptoms depend on localization of strokes
Dementia with Lewy bodies	Histologically indistinguishable from Parkinson disease: alpha-synuclein-containing Lewy bodies occur in the brainstem, midbrain, olfactory bulb, and neocortex. Alzheimer pathology may coexist.	• Cognitive dysfunction, with prominent visuospatial and executive deficits • Psychiatric disturbance, with anxiety, visual hallucinations, and fluctuating delirium • Parkinsonian motor deficits with or after other features • Cholinesterase inhibitors lessen delirium; poor tolerance of many psychoactive medications, including neuroleptics and dopaminergics
Frontotemporal dementia (FTD)	Neuropathology is variable and defined by the protein found in intraneuronal aggregates. Tau protein, TAR DNA-binding protein 43 (TDP-43), or fused-in-sarcoma (FUS) protein account for most cases.	• Peak incidence in the sixth decade; approximately equal to Alzheimer disease as a cause of dementia in patients under 60 years old • Familial cases result from mutations in genes for tau, progranulin, or others **Behavioral variant FTD** • Deficits in empathy, social comportment, insight, abstract thought, and executive function • Behavior is disinhibited, impulsive, and ritualistic, with prominent apathy and increased interest in sex or sweet/fatty foods • Relative preservation of memory • Focal right frontal atrophy • Association with amyotrophic lateral sclerosis **Semantic variant primary progressive aphasia** • Deficits in word-finding, single-word comprehension, object and category knowledge, and face recognition • Behaviors may be rigid, ritualistic, or similar to behavioral variant FTD • Focal, asymmetric temporal pole atrophy **Nonfluent/agrammatic variant primary progressive aphasia** • Speech is effortful with dysarthria, phonemic errors, sound distortions, and poor grammar • Focal extrapyramidal signs and apraxia of the right arm and leg are common • On a diagnostic and pathological continuum with corticobasal degeneration • Focal left frontal atrophy

Genetic factors play an important role in the case of Alzheimer's disease, individuals with apolipoprotein Ɛ4 (APO Ɛ4) have susceptibility to Alzheimer's disease. Individual carriers 1 APO Ɛ4 allele have a risk of suffering from Alzheimer's disease 2-3x higher, when carrying 2 APO Ɛ4 alleles have a much higher risk of 16x than non-carriers. Several risk factors other than family history, including (1) gender (more vulnerable women), (2) history of head injury, (3) individuals with low quality of education, (4) diabetes mellitus , (5) dyslipidemia, (6) Hypertension, (7) low fruit and vegetable diet and lack of activity (Seely and Miller, 2015). Table 2 shown clinical manifestation of alzheimer's disease.

Table 2. Clinical Manifestation of Alzheimer's Disease (Slattum, swerdlow, and Hill, 2011).

General

- The patient may have vague memory complaints initially, or the patient's significant other may report that the patient is "forgetful." Cognitive decline is gradual over the course of illness. Behavioral disturbances may be present in moderate stages. Loss of daily function is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)
- Impaired executive function

Noncognitive

- Depression, psychotic symptoms (hallucinations and delusions)
- Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)

Functional

- Inability to care for self (dressing, bathing, toileting, and eating)

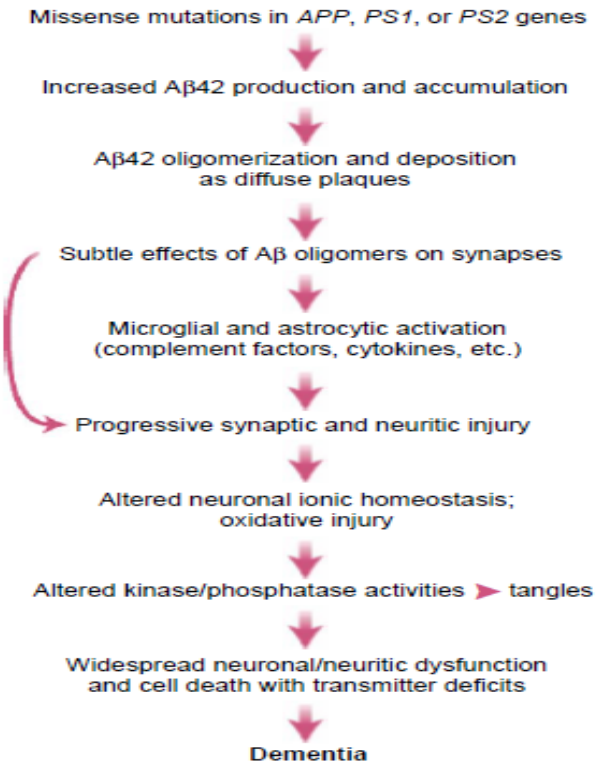
III. PATHOLOGY of ALZHEIMER's DISEASE

Macroscopically, the brains of Alzheimer's patients develop atrophy, especially in the cortical and hippocampal regions. Typical features associated with cerebral atrophy are initiated from the medial temporal lobe, then spread to the lateral and medial parietal, temporal lobe, and lateral frontal cortex. Based on histochemical / microscopic examination can be found neuritic plaque and neurofibrillary tangles. On the cerebrospinal fluid examination, Aβ42 levels can be found low and increased levels of protein tau (Seeley and Miller, 2015). Multiple neurotransmitter abnormalities also contribute to the development of Alzheimer's disease, particularly cholinergic transmission failure. In addition, other neurotransmitter abnormalities such as glutamate, serotonin and substance P are also seen (Sharpe and Lawrie, 2014). In Alzheimer's disease many found acetylcholie-releasing neurons that suffered damage or cell death (Miller, et al., 2008). Oxidative neuronal damage and inflammatory cascades are also involved in disease progression. However, increased amyloid plaque is the most important pathogenesis factor (Imbimbo, Lombard, and Pomara, 2005).

A. Amyloid Cascade Hypothesis

Neuritic plaque or called amyloid plaque is an extracellular lesion found in many brain and vascular tissues, which contain many β-amyloid proteins (Aβ). Aβ is a protein comprised of 39-42 amino acids, a proteolytic product of the transmembrane protein (APP) (Seeley and Miller, 2015). APP is a type 1 transmembrane of glycoprotein produced by many cells, and contributes to secretory or endosomal-lysosomal pathways. Although the physiological function of APP remains unclear, but ubiquitous expression during tissue development indicates that APP has a role in cellular physiology. Some developing theories suggest that APP has a role in (1) neurite outgrowth synaptogenesis, (2) synaptic plasticity, (3) promotion of neuronal cell survival, (4) regulation of cell movement (Imbimbo, Lombard, and Pomara, 2005). The proteolytic pathway of APP is divided into two paths, (1) nonamyloidgenic, the enzyme acting as α-secretase (ADAM 10 or ADAM 7) and releasing transmaprant fragments of sAPPα, and (2) amyloidogenic, the enzyme acting β-secretase (BASE) and release sAPPβ (Imbimbo, Lombard, and Pomara, 2005; Seeley and Miller, 2015). sAPPα is soluble secreted, which shows similarities with growth factors that can increase proliferation and embryonic neural stem cells, but also have neuroprotective function (Imbimbo, Lombard, and Pomara, 2005). The next step is cutting the remaining fragments by the γ-secretase enzyme. The result of cutting C99 (β-secretase product) by γ-secretase is Aβ, excess Aβ42 production is the key and initiator of the development of Alzheimer's disease (Imbimbo, Lombard, and Pomara, 2005; Seeley and Miller, 2015).

Aβ42 aggregation in the form of oligomers (in the early stages) is already neurotoxin and can cause cellular dysfunction. At a later stage, Aβ42 will form amyloid polymerization and fibril formation which will eventually form a neuritic plaque. Neuritic plaque contains central core of amyloid, proteoglycans, Apo Ɛ4, α-antichymotrypsin, and several other proteins. The accumulation of Aβ in the cerebral vascular is known as amyloid angiopathy (Seeley and Miller, 2015). Picture 1 shown pathophysiology of alzheimer's disease.



Picture 1. Pathophysiology of Alzheimer's Disease (Imbimbo, Lombard, and Pomara, 2005).

IV. TREATMENT of ALZHEIMER's DISEASE

Treatment for Alzheimer's disease to date has been limited to cognitive symptoms, there is no treatment aimed at treating (curative) or overcoming the major problems that cause Alzheimer's (amelioration). This provides an opportunity for new drugs aimed at curative purposes in Alzheimer's disease. Cholinesterase inhibitor drugs such as donepezil, rivastigmin, galantamine and memantine (NMDA receptor antagonist) are approved by the FDA (Food and Drug Administration) for the treatment of Alzheimer's disease. All these drugs are limited to symptomatic relief and maximize the patient's ability to independence, but can not prevent disease progression (Winslow *et al*., 2011 ; Seeley and Miller, 2015 ; Aminoff and Kerchner, 2016). Table 3 shown drug recommendation for alzheimer's disease

Table 3 Drug Recommendation for Alzheimer's Disease (Winslow, et al., 2011)

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Acetylcholinesterase inhibitors are modestly effective in patients with mild to moderate Alzheimer disease, although limited by their adverse effects.	A	12
Combination therapy with an acetylcholinesterase inhibitor and memantine (Namenda) should be considered in patients with moderate to severe Alzheimer disease.	B	27
Atypical antipsychotic agents can improve some behavioral manifestations of Alzheimer disease but are associated with increased mortality in older patients.	B	31, 33
Nonsteroidal anti-inflammatory drugs, vitamin E, testosterone, estrogen, statins, and insulin sensitizers are not recommended for the treatment of Alzheimer disease.	B	34-43, 46-49
Physicians should consider discontinuing treatment for Alzheimer disease in patients who continue to decline despite maximal therapy.	C	16

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

V. DRUG DEVELOPMENT In ALZHEIMER's DISEASE

Many potential new therapeutic / pharmacologic agents, still in the process of research or investigation until today. Nearly most of the focus of research for new drugs in the field of Alzheimer's is related to the modification of disease pathologic processes ie the decrease in amyloid plaque (Winslow, et al., 2011). Some of the newer drugs that develop include: (1) drugs that reduce the production of Aβ (β-secretase inhibitors, γ-secretase inhibitors, α-secretase activators), (2) drugs that prevent Aβ aggregation, (3) drugs inducing Aβ clearance, (4) drugs with target Ƭ-protein (Mangialasche, et al., 2010). A study related to the effectiveness of γ-secretase inhibitors (terenflurbil and semagacestat), both showed unfavorable results. Even for semagacestat showed an accelerated decline in cognitive function compared to placebo (Seeley and Miller, 2015). The use of immunotherapy that directly affects on Aβ also does not provide good results in phase III (Aminoff and Kerchner, 2016).

A. Verubecestat (β-secretase inhibitor): Alzheimer's Association International Conference (AAIC), the researchers reported that the β-secretase inhibitor drug could significantly decrease Aβ levels in mild-moderate Alzheimer's. Verubecestat is a class of β-secretase inhibitor (BACE1 inhibitor) drug that is included in phase 3 clinical trial. There were two clinical trials in phase 3 for verubecestat (1) a study of more than 2000 patients with mild-moderate Alzheimer's, and (2) a study of 1500 patients with Alzheimer's prodrome and mild cognitive impairment (alz.org | reseacrh center). The β-secretase enzyme known as β-site APP cleaving enzyme (BACE) has two similarly structural homologues namely BACE1 and BACE2. Both homologues have the same activity related to cuts in APP. The difference in the amount of BACE2 in the cerebral (nerve cells) is not so much, whereas BACE1 is much expressed in neurons. An in vivo study has been conducted to prove and ensure that BACE1 is the principal β-secretase enzyme present in CNS, and BACE2 does not compensate for the missing BACE1 function in producing Aβ in CNS (Vassar, 2014). In addition, the other difference lies in the enzymatic specificity between the two. Research using mouse models, BACE1 deficiency condition showed a decrease of Aβ production, whereas BACE2 deficiency did not show significant difference of Aβ production (Yan, 2016).

A study suggests that the proteolytic site of BACE1 may also work on other human aspartic proteases (other than BACE1) (other than APP). This allows the use of BACE1 inhibitors to interfere with physiological function, excluding the effect of reducing the production of Aβ (Vassar, 2014; Yan, 2016). For example BACE1 activity in

neurogilin 1 (NRG1) will release epidermal growth factor (EGF) which can bind to ErbB receptor in schwann cell (myelinization stimulation). The use of BACE1 inhibitors is likely to cause hypomyelination. Although the decrease in BACE1 activity on some other substrates may decrease its physiological function, but for other substrates it may even improve its physiological function. For example Jag1 is one of the substrates of BACE1, the decrease in BACE1 activity leads to an increase in Jag1 levels, the effect being increased stimulation of astrogenesis and neurogenesis (Vassar, 2014). Verubecestat (MK-8931) is the first class BACE1 inhibitor drug to be included in phase 3 clinical trial. Verubecestat has an amidine group that can bind to the catalytic site of BACE1 by hydrogen bonding (Kennedy, et al., 2016).

VI. CONCLUSION

Treatment for Alzheimer's disease to date has been limited to cognitive symptoms, there is no treatment aimed at treating (curative) or overcoming the major problems that cause Alzheimer's (amelioration). This provides an opportunity for new drugs aimed at curative purposes in Alzheimer's disease. BACE1 inhibitor drug has been developed and provides an opportunity to be used in treating Alzheimer's disease.

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