Review Article

Flortaucipir F 18 for Diagnosis of Alzheimer's Disease: A Review

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Abstract

Alzheimer's disease (AD) development begins years before clinical diagnostic confirmation. Approaches to advance detection can provide chances for prompt intervention, symptomatic treatment, and better patient functionality. AD is generally diagnosed based on clinical features with evident CT scan findings. CT brain shows cerebral atrophy and the ventricles that contain cerebrospinal fluid are noticeably enlarged. These findings are suggestive but nonspecific because these abnormalities are also present in other illnesses and people with normal age-related changes. Cerebrospinal fluid (CSF) analysis for low beta-amyloid 42 and elevated tau together with mental status and neuropsychological testing is helpful in the diagnosis of the preclinical stage. The advancement of flortaucipir positron emission tomography (PET) scans in detecting tau-containing neurofibrillary tangles in the brain helps in early diagnosis and differentiation of tau containing neuropathological diseases. Furthermore, it

can differentiate tau pathologies in non-AD patients. This review highlights the uses of flortaucipir F 18 in AD patients and the mechanism of this PET tracer evaluating its safety profile.

Keywords: Alzheimer's Disease

1. Introduction and Background

Dementia is a common term that refers to a deterioration in the cognitive ability of an individual, severe enough to cause interference with activities of daily living. Alzheimer's disease (AD) is a progressive brain disorder that destroys memory and cognition irreversibly and is the most prevalent type of dementia. In most people with AD, symptoms first appear insidiously in their mid-60s, which include progressive impairment of cognitive and behavioral functions including comprehension, memory, attention, language, reasoning, and judgment [1]. Estimates vary, but experts suggest that more than 5.5 million Americans, most of them age 65 or older, may have dementia caused by AD. It is also the sixth leading cause of mortality in the United States. Currently, there is no known cure for AD, but there are medications and treatments available that may slow the progression of the disease and improve some symptoms. The symptoms of AD correspond to the stage of the disease. Biomarker tests for AD have shown at least moderate sensitivity and specificity of 0.50 or higher. Objective evidence with cognitive impairment is needed to support an Alzheimer's dementia diagnosis [2].

Aggregates of tau containing neurofibrillary tangles and amyloid plaque composed largely of aggregated amyloid-β (Aβ) fragments are observed in the medial temporal lobe and hippocampus in the pathology of AD [3]. AD can be diagnosed without histopathological examination with the advent of biomarkers that enable in vivo identification of underlying AD, in the presence of evident clinical features [4]. Wide ranges of neurodegenerative disorders are caused by the pathological accumulation of aggregated hyperphosphorylated tau protein in neurons and glia [5]. Tau is an intracellular protein that regulates intracellular transport, binds to and stabilizes axonal microtubules in neurons, thereby regulating intracellular transport [6]. It has been observed that the cortical Aβ plaque, correlates more closely with AD-associated cognitive impairment and neurodegeneration in which phosphorylated tau aggregates in neurofibrillary tangles (NFTs). Thus, an imaging biomarker for pathological tau could benefit theoretically in the diagnosis and selection of patients for therapy as well as allow for monitoring disease progression and the response to putative disease-modifying treatments.

2. Review

A minimally invasive estimate of the neuropathological features of AD has been provided by PET ligands, such as Aβ neuritic plaque deposition [7]. Flortaucipir F 18 is being established as a PET tracer for the detection of the aggregated tau of AD. In vitro autoradiography studies of brain tissue from symptomatic patients with AD have found that the flortaucipir F 18 signal correlates with the level of paired helical filament tau by immunohistochemistry and binds with a dissociation constant in approximately the 0.5 nm. range [2]. Flortaucipir F 18 is a radioactive diagnostic agent indicated for PET imaging of the brain to estimate the density and distribution of aggregated tau NFTs in adult patients with cognitive impairment who are being evaluated for AD. Feisher et al. noted that the full autopsy data set included 26 impaired participants with a non-Alzheimer clinical diagnosis, of which 19 had less than high levels of AD neuropathologic change (ADNC) at autopsy [8]. In another study by Wang et al. in 16 of the 19 patients, flortaucipir F 18 PET images were accurately interpreted as not being consistent with

an Alzheimer's pattern [9]. Flortaucipir F 18 is a diagnostic radioactive agent for PET imaging of the brain, which may be used to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) in patients who are being evaluated for AD with cognitive impairment. It was approved for use in patients being evaluated for AD on June 1, 2020, by the Food and Drug Administration [7]. The presence of both beta-amyloid neuritic plaques and tau NFTs in the brain is required for the neuropathological diagnosis of AD. To appreciate tau NFTs in the brain, flortaucipir F 18 is the first and only approved diagnostic agent. It can help in the diagnosis of early AD as it can interpret images based on the pattern and density of the radioactive signal within the neocortical gray matter. Off-target binding is seen in the choroid plexus, striatum, and brainstem nuclei. Uptake of tracer in the neocortical grey matter regions contributes to scan interpretation [8].

A positive scan shows increased neocortical activity in the posterolateral, temporal, occipital, or parietal region(s), with or without frontal activity. A negative scan shows no increased neocortical activity, increased neocortical activity only to the mesial temporal, anterolateral temporal, and/or frontal regions [8]. on-AD tau pathologies such as those seen in frontotemporal dementia, progressive supranuclear palsy, cortico-basal, and chronic traumatic encephalopathy have poor binding to flortaucipir F 18. Cortical PET signal from flortaucipir in patients with dementias other than AD is usually lower than expected in typical patients with AD and, when present, tends to be greatest in anterior temporal lobes. In general, these non-AD clinical diagnosis cases support the high specificity of PET imaging with flortaucipir for distinguishing AD from non-AD tau pathologies. The use of flortaucipir F 18 is generally considered safe [9]. The safety and effectiveness of flortaucipir F 18 was evaluated in two clinical studies. Five evaluators read and interpreted the imaging results in each study. The inspectors were blinded to clinical information and interpreted the imaging as positive or negative [10]. However, definitive data regarding the toxicity of flortaucipir F 18 is not available. Some patients experienced an increased risk of severe adverse effects such as headaches and hypertensive urgency due to overdose. Symptomatic and supportive measures are recommended in case of overdose or adverse effects [11, 12].

3. Conclusions

The use of flortaucipir F 18 in studies of tau PET has the potential for evaluation of neuropathologies and clinical detection of NFTs in patients with AD pathology. There is a strong correlation between the imaging process of neurodegeneration and tau PET, the role of tau PET with respect to AD pathology will be critical to establishing. These developments could lead to more accurate disease staging in terms of tau burden and evaluation of putative therapies.

Conflict of Interest

The authors declare no conflict of interest

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