alzheimer's research&therapy

COMMENTARY

Amyloid imaging in clinical trials

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Abstract

The possibility to map amyloid-beta, the Alzheimer's disease hallmark protein, in vivo opens the application for amyloid imaging in clinical trials with disease-modifying agents. Monitoring change in amyloid burden, particularly when potential amyloid-lowering drugs are at play, requires accurate analytical methods. Studies to date have used suboptimal methods that do not account for heterogeneous changes in flow associated with disease progression and potentially with anti-amyloid drugs. In this commentary, we discuss practical and methodological issues regarding longitudinal amyloid imaging and propose several quantitative, yet feasible, alternatives for reliable assessment of changes over time in amyloid burden.

Introduction

The advent of radiotracers such as [^{11}C]Pittsburgh compound B (PIB), [^{18}F]florbetapir, [^{18}F]flutemetamol and [^{18}F]florbetaben in combination with positron emission tomography (PET) allows in vivo detection of fibrillar amyloid plaques, one of the neuropathological hallmarks of Alzheimer's disease (AD). Amyloid imaging is a helpful diagnostic tool and can also serve as a secondary outcome measure in AD clinical trials with disease-modifying agents such as the anti-amyloid monoclonal antibodies bapineuzumab and solanezumab [1,2].

The recently completed bapineuzumab phase III study showed no clinical effect, but AD patients in the treatment arm showed less increase in PIB-PET retention over 71 weeks compared with the placebo group [3]. This observation may be interpreted as target engagement of the bapineuzumab treatment, resulting in less accumulation of brain amyloid. In this commentary we question whether this difference in PIB retention over time truly reflects differences in amyloid burden change or (partially) represents an artifact introduced by a suboptimal method, namely the standardized uptake value ratio (SUVr), for longitudinal data analysis. We discuss the methodological considerations for reliable longitudinal amyloid imaging and propose alternative quantitative approaches for future clinical trials.

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Dynamic versus static positron emission tomography scans

PET enables in vivo visualization and quantification of physiological and pathophysiological processes by injecting positron emitting radionuclides that bind specifically to a target tissue. In essence, amyloid PET scans can be acquired by monitoring the time course of the radiotracer distribution during the entire scan after injection into the camera (that is, dynamic scanning) or by selecting a specific time interval (for example, between 60 and 90 minutes) after injection (that is, static scanning). Dynamic scans allow for quantification of specific binding by taking into account between-subject differences of tracer delivery and clearance rates. The kinetic models most often used to analyze dynamic scans are receptor parametric mapping [4] and reference Logan [5], with the nondisplaceable binding potential and the distribution volume ratio as outcome measures, respectively. Static scans after a bolus injection of the tracer are semiquantitative because they are usually analyzed using the SUVr, without taking into account many nuisance variables that influence tracer uptake.

Head-to-head comparison of the analytical methods for both cross-sectional and longitudinal data showed that dynamic scans are superior to static scans in terms of accuracy, test–retest variability and image contrast [6,7]. Among dynamic scan protocols, receptor parametric mapping is preferred over the Logan distribution volume ratio due to better test–retest performance and lower susceptibility to statistical noise [6,8]. The assets and disadvantages of dynamic and static approaches are summarized in Table 1.

Table 1 Assets and disadvantages of dynamic and static scanning

	Dynamic scanning	Static scanning
Scan duration	–	+
Computational simplicity	–	+
Test–retest variability	+	–
Accuracy	+	–

Longitudinal amyloid imaging in clinical trials

Owing to the relative short scan duration and computational simplicity of the SUVr, it is tempting to select the SUVr as the analytical method in clinical trials with large sample sizes. In AD patients, however, the SUVr overestimates true binding (16% on average) and this systematic error is inconsistent over time [7]. This overestimation is largely due to differences in tracer delivery in target regions (that is, cortex) relative to that in the reference region (usually the cerebellum). As AD progresses, cerebral blood flow will decrease most prominently in cortical regions and not so much in the cerebellum [9]. These heterogeneous flow effects can cause an artificial lowering of the SUVr that may be incorrectly interpreted as decreased amyloid load. Importantly, these flow changes may differ between patients treated with amyloid-lowering drugs and the placebo group, and therefore may lead to true bias. Heterogeneous flow effects do not hinder receptor parametric mapping and reference Logan as a correction is implemented in these kinetic models.

AD trials are shifting towards including patients earlier in the disease course; that is, in the prodromal or even preclinical stage of AD. The reason for this earlier inclusion is twofold. First, according to the amyloid hypothesis, deposition of amyloid-beta is the first step in the amyloid cascade, and it seems reasonable that by stopping this process one may prevent its deleterious effect. Second, results from large phase III trials in mild to moderate stages have been disappointing, and could be summarized as 'too little, too late'. One might argue that blood flow reductions are less prominent in these earlier disease stages and thus the SUVr could suffice. Indeed, the bias may be smaller in mildy cognitive impaired patients, healthy older patients and asymptomatic mutation carriers if compared with demented patients. Accurate quantification, however, is also of utmost importance in these groups because during the time course of clinical trials subjects may progress to more advanced stages accompanied by substantial heterogeneous flow changes.

Another reason why dynamic scanning should be preferred over static scanning is that the anti-amyloid drugs themselves may cause changes in cerebral blood flow and thus tracer delivery. Substantial numbers of patients treated with anti-amyloid drugs show signs of cerebral amyloid angiopathy (for example, microbleeds) [10], suggesting that the breakdown of amyloid plaques is followed by clearance via vascular pathways. Vascular amyloid load, as well as inflammatory reactions associated with the removal of brain amyloid, could affect tracer delivery by reducing cerebral blood flow. This should be taken into account by the analytical models used to quantify amyloid load. As long as the underlying mechanisms of therapeutic agents are not fully understood, quantitative analytical methods should be preferred over the SUVr. If these methods are not preferred, there will remain uncertainty over whether we are looking at a genuine lowering of amyloid plaque burden over time or just an artificial decrease of tracer uptake.

Alternative approaches for dynamic scanning

Arguments against performing dynamic scans are the demanding scanning protocol and the more complicated data analysis. A practical solution for the latter is to perform dynamic scans at multiple sites and to assign one specialized center to conduct the data analysis. We have previously shown that it is feasible to perform a large number of dynamic (90 minutes) [^{11}C]PIB scans in a single center [11]. An alternative to large-scale phase II and III imaging studies using only the SUVr could thus be to perform smaller proof-of-concept studies in specialized PET centers with extensive experience in dynamic PET scanning. Alternatively, the duration of dynamic scan protocols could potentially be shortened in at least two ways. First, a bolus injection followed by continuous infusion could be administered to generate a steady state [12]. During steady state, the SUVr is equivalent to nondisplaceable binding potential and thus scanning for a short(er) time interval would suffice. This method has yet to be validated for current amyloid tracers. Second, head-to-head comparisons between recently developed amyloid radiotracer [^{18}F]AZD-4694 and [^{11}C]PIB revealed an almost perfect correlation [13]. [^{18}F]AZD-4694 has the benefit of quickly reaching equilibrium. Using [^{18}F]AZD-4694, accurate quantitative data collection can potentially be completed within 50 minutes.

Conclusion

Clinical trials aiming to assess changes in amyloid burden after administering an anti-amyloid drug should select a dynamic amyloid imaging protocol.

Abbreviations

AD: Alzheimer's disease; PET: Positron emission tomography; PIB: [^{11}C]Pittsburgh compound B; SUVr: Standardized uptake value ratio.

Competing interests

The authors declare that they have no competing interests.

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