Annals of Nuclear Cardiology Vol. 9 No. 1 91–93

REVIEW ARTICLE

Progress of ^{18}F-flurpiridaz in Clinical Trials

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Received: October 6, 2023/Accepted: October 9, 2023

Abstract

^{18}F-flurpiridaz is a novel positron emission computed tomography (PET) tracer in ongoing clinical trials in United States and Japan. A phase III prospective, open-label, multi-center study to assess the feasibility of ^{18}F-flurpiridaz was reported by Maddahi et al. in patients with known or suspected coronary artery disease (CAD) in 2020 in United States (1). ^{18}F-flurpiridaz binds to mitochondrial complex 1 and would distribute to the myocardium with its higher extraction fraction than those in single-photon emission computed tomography (SPECT) tracers (2). In that phase III trial, 795 participants with known or suspected CAD showed that sensitivity of ^{18}F-flurpiridaz PET (for detection of ≥50% stenosis by invasive coronary angiography) was 71.9%, significantly ($p < 0.001$) higher than ^{99m}Tc labeled SPECT agent (53.7%), while specificity did not meet the prespecified noninferiority criterion (76.2% vs. 86.6%, p=NS) (1). Therefore, a second phase III Food and Drug Administration trial was planned and completed by GE Healthcare. Late phase II open-label multicenter study of PET scan using ^{18}F-flurpiridaz (named NMB58 in Japan) to assess myocardial blood flow and diagnostic feasibility in patients with known or suspected CAD started in Japan of 2023.

Keywords: Coronary artery disease, Coronary flow reserve, Myocardial perfusion, PET, Tracers
Ann Nucl Cardiol 2023; 9 (1): 91–93

Necessity of new tracers for PET imaging

For more than 25 years, ^{99m}Tc-labeled tracer (^{99m}Tc-sestamibi or -tetrofosmin) for myocardial perfusion single-photon emission computed tomography (SPECT) have been used to diagnose coronary artery disease (CAD), determine indications for coronary interventions, and confirm recovery after invasive or non-invasive treatment. In Japan, ^{201}Tl has been widely used for myocardial perfusion imaging due to its simplicity of a single intravenous injection during exercise or pharmacological stress. Because of the high radiation exposure of ^{201}Tl and the fact that ^{99m}Tc tracer can be easily extracted from a generator at each facility, the ^{99m}Tc agents have been used as the standard protocols. However, the negative effects of extra cardiac accumulation including in the liver and gut, and a slightly lower myocardial extraction fraction compared to ^{201}Tl are of simple concerns. As Rozanski et al. reported, from the 1990s to 2009, the proportion of cases with abnormal SPECT and the amount of stress-induced ischemic myocardium continued to decrease (3). This situation has also been confused in recent years by the rise of non-obstructive coronary artery diseases that cannot be diagnosed without myocardial perfusion imaging, such as ischemia with non-obstructive coronary arteries. Therefore, the necessity of a new tracer for more accurate diagnosis of CAD, and the measurement of coronary flow reserve (CFR) which plays an important role for determining patient prognosis and indications for treatment, have led to a focus on positron emission tomography (PET) perfusion agents (4, 5).

Characteristics of ^{18}F-flurpiridaz

Characteristics of ^{18}F-flurpiridaz and other myocardial PET tracers are as follows, production; regional cyclotron, treadmill exercise; available, kinetics; binds mitochondrial complex 1, mean positron range in tissue; 0.1 mm, data acquisition; dynamic and static, radiation dose; 5-6 mSv (effective dose for rest/ stress common protocol), flow quantification; very good, and Food and Drug Administration (FDA) approval; not yet (6). It has a half-life of 110 minutes and can be delivered in the same manner as ^{18}F-fluorodeoxyglucose. Notably, ^{18}F-flurpiridaz's first pass myocardial extraction fraction is 94% which is close to 100% of ^{15}O H_2O PET tracer. The image quality is rated as excellent.

DOI: 10.17996/anc.23-00011

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The estimated radiation dose is also lower than that for the regular rest/ stress protocol with ^{99m}Tc tracers.

In animal model, tracer kinetics of ^{18}F-flurpiridaz was confirmed by Bengs et al. They concluded that a simplified assessment of relative myocardial perfusion and CFR, based on imaged-derived tracer uptake is feasible with ^{18}F-flurpiridaz in mice and follows a two-tissue compartment model (7).

Clinical utilities of ^{18}F-flurpiridaz

In that phase III trial by Lantheus Medical Imaging, 795 participants with known or suspected CAD showed that sensitivity of ^{18}F-flurpiridaz PET (for detection of ≥ 50% stenosis by invasive coronary angiography) was 71. 9%, significantly ($p<0.001$) higher than ^{99m}Tc labeled SPECT agent (53. 7%), while specificity did not meet the prespecified noninferiority criterion (76.2% vs. 86.6%, p=NS) (1). They showed receiver-operating characteristic curve analysis demonstrated superior discrimination of CAD by ^{18}F-flurpiridaz PET versus ^{99m}Tc labeled SPECT in the overall population, in women, obese patients, and patients undergoing pharmacological stress testing ($p<0.001$) (1). They concluded that ^{18}F-flurpiridaz PET imaging was superior to SPECT imaging for defect size ($p<0.001$), image quality ($p<0.001$), diagnostic certainty ($p<0.001$), and radiation exposure (6.1 ± 0.4 mSv vs. 13.4 ± 3.2 mSv, $p<0.001$). ^{18}F-flurpiridaz PET was safe and well tolerated.

The feasibility and diagnostic performance of segmental or coronary territory myocardial blood (MBF) flow of ^{18}F-flurpiridaz was reported by Packard et al (8). They concluded that measurement of stress MBF, myocardial flow reserve, and relative flow reserve at the segmental level with ^{18}F-flurpiridaz enhances overall flow-based diagnostic performance for the detection of both ≥ 50% and ≥ 70% of coronary stenosis compared with standard assessments of these same metrics at the coronary territory level. In another study, diagnostic performance was compared between blinded visual assessment and blinded derivations of automated relative quantification (9). Both methods achieved comparable accuracy for the detection of global CAD, reaching 71% and 72% by visual analysis, and 72% and 68% by automated quantification using CAD ≥70% or ≥50% stenosis for standard of truth (9).

The diagnostic performance of ^{18}F-flurpiridaz was based on assessment of relative perfusion imaging following the conventional invasive coronary angiography. However, the diagnostic performance may improve if other myocardial perfusion imaging variables such as myocardial blood flow or CFR (10). Furthermore, if another standard of truth such as invasive fractional flow reserve or instantaneous wave-free ratio was used for the assessment of functional ischemia, diagnostic accuracy may improve.

Importantly, ^{18}F-flurpiridaz could not show the specificity meet the prespecified noninferiority criterion (76. 2% vs. 86.6%, p=NS), therefore, a second phase III FDA trial was planned and completed by GE Healthcare (Assessing myocardial perfusion in suspected coronary artery disease: rationale and design of the second phase 3, open-label multicenter study of flurpiridaz (F-18) injection for PET imaging; NCT03354273) (11). Officially, there is no further information about a second phase III trial, but the results are being presented at the American Society of Nuclear Cardiology conference in 2022 and the Society of Nuclear Medicine and Molecular Imaging conference in 2023.

Conclusions

^{18}F-flurpiridaz is a novel and very promising myocardial perfusion PET tracer which may be launched in United States in near future.

Acknowledgments

None.

Sources of funding

None.

Conflicts of interest

Dr. Naoya Matsumoto received a consultant fee from Nihon Medi-physics as a principal clinical investigator of NMB58.

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