18F Flurpiridaz Shows Promise as a Diagnostic Imaging Agent for CAD

GE Healthcare and Lantheus Holdings, Inc. (NasDAQ: LNTH), parent company of Lantheus Medical Imaging, Inc. (collectively “Lantheus”), have begun a second Phase 3 clinical trial of 18F-flurpiridaz injection PET myocardial perfusion imaging (the AURORA study; NCT03354273) for the detection of coronary artery disease (CAD), the most common form of heart disease. CAD affects an estimated 15.5 million Americans 20 years of age or older and is the leading cause of death in the United States and Europe.1

As per ASNC 2016 Guidelines, “rest-stress myocardial perfusion PET is recommended for patients with suspected active CAD, who meet appropriate criteria for a stress imaging test, and who also meet one or more of the following criteria:

1. prior stress imaging study that was of poor quality, equivocal or inconclusive
2. high-risk patients
3. those with body characteristics that commonly affect image quality including large breasts, breast implants, and obesity (BMI greater than 30),” as well as other characteristics.2

An 18F-flurpiridaz injection is an 18F-labeled novel investigational diagnostic tracer undergoing development for PET myocardial perfusion imaging (MPI) in those with suspected coronary artery disease. A total of 1,012 patients have been administered an 18F-flurpiridaz injection over the course of three Phase 1, one Phase 2, and one Phase 3 studies. Results of the Phase 2 study have been reported elsewhere,3 and results of the first Phase 3 study have been submitted for publication.

The AURORA study is an international multicenter study to evaluate diagnostic efficacy of 18F-flurpiridaz injection PET MPI in the detection of CAD. In this prospective, open-label study, patients with suspected coronary artery disease, for whom an intracoronary angiography has been indicated, will undergo a SPECT MPI and 18F-flurpiridaz injection PET MPI prior to the performance of coronary angiography. The primary endpoint is the diagnostic efficacy (sensitivity and specificity) of 18F-flurpiridaz injection PET MPI for the detection of significant CAD, with the secondary endpoint being the diagnostic performance of 18F-flurpiridaz injection PET MPI compared to SPECT. The study was officially launched on June 8, 2018, and is actively enrolling. A total of 650 patients will be enrolled in the study with the last patient enrollment—last patient follow-up projected to occur around August of 2020.

References
Radiotherapy for Cardiac PET Imaging

David W. Dick, PhD, Chief of Radiolucides Production & PET Radiophysics, University of Iowa

The clinical value of cardiac positron emission tomography (PET) imaging with nitrogen-13 was demonstrated more than 20 years ago, but the requirement of a cyclotron within the imaging facility, radioactive pharmaceutical expense, and the lack of reimbursement for clinical PET studies were barriers to its widespread use. Advances in medical imaging technology have led to an increased demand for radiopharmaceuticals that provide early and accurate diagnosis of cardiac function and disease states. The latest advances in PET/CT equipment have reduced patient dose while improving imaging quality, and simultaneous assessment of both anatomy and perfusion by PET/CT can result in improved diagnostic accuracy. The PET-mycardial perfusion imaging (MPI) allows accurate measurement of myocardial perfusion, absolute myocardial blood flow and function at stress and rest in a single study session performed in approximately 30 minutes. Dynamic myocardial blood flow analysis has demonstrated additional prognostic value beyond relative perfusion imaging. Studies have shown that PET-MPI provides higher diagnostic accuracy than SPECT-MPI for detection of coronary artery disease, having a higher sensitivity and specificity as well as lower radiation dose during a shorter examination time period. Despite this, some insurance companies will not cover the cost of the MPI study without an equivocal positive or negative finding by other diagnostic methods. Various PET tracers are available for MPI, with rubidium-82 chloride or nitrogen-13 ammonia most commonly used. Table 1 lists the half-lives of some PET radioisotopes used in cardiac imaging. The halflife of these cardiac imaging agents and their sensitivity to specific disease states determines their use in cardiac PET protocols. The known tracer kinetics of PET radiopharmaceuticals, along with the advantages of PET (e.g., attenuation correction, high temporal resolution), allow absolute quantification of myocardial blood flow. This provides an improved diagnosis of coronary artery disease. Access to the right agents is still a barrier for some facilities, although the development of radionuclide generators replaces the need of a cyclotron in some cases. The main disadvantage of the available tracers is cost, and the continual use to work with Cardiac Medicine and Medical Services (CMS) and insurance companies for reimbursement.

Table 1

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<thead>
<tr>
<th>Radionuclide</th>
<th>Halflife (minutes)</th>
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<tbody>
<tr>
<td>82Rb</td>
<td>80.6</td>
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<tr>
<td>82Rb</td>
<td>80.6</td>
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<tr>
<td>18F</td>
<td>109.8</td>
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<tr>
<td>15O</td>
<td>9.97</td>
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<tr>
<td>15O</td>
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References:
CTN Highlights

CTN is once again partnering with other SNMMI centers and councils to offer valuable information to assist you in your practice. In addition to the general nuclear medicine sessions, a special track on cardiovascular imaging discusses current practices, presents interesting and puzzling cases, and explores what’s on the horizon. CTN is sponsoring the two sessions listed below as part of the General Nuclear Medicine track.

Friday, January 18

- 8:00-10:00 am: Theranostics Agents Beyond Lutathera: What’s New and What’s on the Horizon
- 10:15 am-12:15 pm: Nuts and Bolts of Using PRRT

CTN 2019 Summer Webinar Series

The 2019 webinar series is focused on a review of radiopharmaceuticals used in imaging. This includes, in some cases, both PET and SPECT imaging. In addition to the topics provided below, one webinar will be dedicated to radiotherapies and new agents on the horizon.

Disciplines:
- Bone
- Infection
- Neurology
- Nuclear Cardiology
- Oncology
- Pediatrics

CTN will update the webinar information as speakers and dates are confirmed. Please check the CTN website in 2019 for the final schedule.

Tech Talk

Monitoring Essentials of Clinical Trials Involving Radiopharmaceuticals

Ing-Mari Bahr, CNMT, President;
Robert Dann, Sr. CRA;
Lisa Hall, RTR(P) NR, Sr. CRA;
Terri Clark, VP Global Clinical Operations
Trial Care International, LLC

All clinical trials are highly regulated and are usually monitored onsite by experienced clinical research associates (CRAs). What we have found, after years of being involved in clinical trials, is that the experience of the CRA is of most importance when the trial involves a radiopharmaceutical, either as the investigational agent, such as a new cancer imaging agent or therapeutic, or as a measure of the clinical endpoint, such as an FDG PET scan. Only a small percentage of CRAs are qualified and prepared to provide the additional level of review imposed by the nature of radiopharmaceuticals. A trained nuclear medicine/radiology technologist, with the appropriate experience, may want to consider becoming a CRA.

As a clinical research organization (CRO) specializing in imaging/radiotherapeutics/theranostics, with more than 100 years in the field combined, we present a brief overview of areas identified as important when monitoring a clinical trial with imaging components.

Site Identification: In the process of selecting a site for this type of trial, it is essential for the CRA to:
- understand the path of adding a new isotope to the current RAM license;
- evaluate imaging equipment and software to be used;
- confirm proper quality control (QC) evaluation of images before site selection and ongoing throughout study;
- evaluate appropriate location for IP reconstitution and administration such as lead-lined walls, etc.;
- ensure access to any and all correlative imaging modalities and coordination with other departments.

During the Study: The CRA performs a number of vital tasks directly related to imaging that include:
- image evaluation to ensure quality, correct anatomy imaged, processing, and imaging protocol compliance, and feedback on quality and technique;
- training onsite readers and technologists;
- providing onsite imaging support for the first few subjects imaged;
- providing technologist support off-site;
- reviewing appropriate blinded reads and select and train blinded readers, and ensure proper conduct of blinded reads.
- training onsite by experienced clinical research associates (CRAs).
- providing training of the staff on dosing to include IP preparation, reconstitution, and administration;
- ensuring appropriate technique and proper accountability and documentation;
- reviews decay correction and dosing rules and proposes radia tion dosimetry-based adjustments; and
- reviews radiobiology questions including implications for additional level of review imposed by the nature of radiopharmaceuticals.

Additional procedures: The CRA also may need to provide guidance and training for the imaging core lab used to establish flow of documents and images, develop the core lab charter and imaging manual, set up blinded reads and select and train blinded readers, and ensure proper conduct of blinded reads.

With the increased of new products using PET imaging to determine imaging endpoints and the development of new radiotherapeutics, a CRA with imaging expertise is of essential value in the execution of a successful clinical trial. If the above skillset aligns with your experience and sounds interesting, becoming a CRA could be a potential career path for you.
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rtifacts can occur in cardiac PET imaging, and I dealt with many of them throughout my years as a clinical Nuclear Medicine Technologist. The most commonly seen are metal artifacts and anatomical misalignment due to patient motion. Motion artifacts can cause an antifactual abnormality resulting in a false positive defect on a cardiac PET image. Here are some tips to avoid these artifacts.

Metal Artifacts: Remove all metal around the neck
- Outpatient: It is best to put the patient in a gown. I’ve found lucky coins and prayer pins on the inside of patient’s shirt that become detectable in the CT attenuation correction scan. I have also learned you can never assume when a patient says their shirt has plastic embellishments. The plastic embellishments are usually made of metal.
- In-patient: An in-patient may have a medicine pump or a heart monitor device that is located in the chest area. While you cannot remove these, it is best to relocate the medical device to either above or below the heart so it will not mask the heart during the scan.

Patient Motion: Encourage relaxation
- Improve patient comfort: Misalignments from motion during a scan can cause a misinterpretation due to degrading imaging quality. Do everything you can to make the patient comfortable before the scan - an extra pillow, a warm blanket, and a cushion underneath their elbows are examples of methods I have used with success.
- Communication: Talk to the patient and explain what will happen. Discuss the instructions for scanning with the patient that may involve a breath hold during the CT attenuation scan so as to reduce misalignment during the PET scan. Also inform the patient of all the side effects that may occur during the pharmacological stress test and urge your patient to remain calm and to communicate with the technologist or nurse if he or she is having a side effect. If the patient feels nervous or is scared, there may be movement during the scan.

Various types of artifacts may occur due to other factors, but these are the most common and the easiest to avoid. While we cannot avoid an implanted metal devices located near the heart a technologist must be aware of these artifacts and anatomical misalignment due to patient motion.

References:

WHAT’S HAPPENING

CTN Internship Program

Internship can be an integral part of the education process in attaining a successful and satisfying career, especially when one is pursuing a pathway in a specialized field. As a Clinical Trials Network (CTN) intern, you are exposed to the multiple components related to clinical research and are expected to participate in projects involved in translating research into the clinic. By helping disparate groups from industry and academia to pool their efforts to moving novel radiopharmaceuticals into the clinical space, you are participating in a rapidly expanding field of theranostics and specialized imaging.

CTN comprises strong leadership and members—physicians, technologists, physicists, radiochemists, and industry—having many years of diverse experience in the field. Through greater standardization of imaging in clinical trials and facilitating the use of novel radiopharmaceuticals to into research projects, CTN directly helps promote the approval of new radiopharmaceuticals and educate users on the use of these tracers. This is a two-year mentorship for those interested in radiopharmaceutical development, clinical translation of approved radiotracers, and image standardization.

The application process is closed for this year, but read about our Internship program at SNMMI CTN Internship Program and click on Internship. If you have questions about the program, please contact CTN at ctncf@snmmi.org.

In the NEWS

AUC for PET Myocardial Perfusion Imaging

Sukhjeet Ahuja, MD, MPH, Director, Evidence and Quality Department, SNMMI

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he 2014 Protecting Access to Medicare Act (PAMA) established a new program under fee-for-service Medicare to promote the use of Appropriate Use Criteria (AUC) for Advanced Diagnostic Imaging Services (ADIS). This covers CT, MRI, and all Nuclear Medicine procedures including PET. PAMA requires referring physicians to consult AUC developed by a Centers for Medicare and Medicaid Services (CMS)-approved Provider Led Entity or “PLE” (usually a specialty society such as SNMMI) to ensure cost-effectiveness and appropriate utilization of ADIS. Under the program, AUC may be developed only by organizations that are deemed to be “qualified provider-led entities” (Q-PLE) by the CMS. After going through a rigorous and extensive application, SNMMI was approved as a Q-PLE in June 2016.

SNMMI modeled its AUC development process after the RAND/UCLA Appropriateness Method,2 including a systematic review of evidence followed by development of AUC for various common clinical scenarios using a modified Delphi approach. This process is also consistent with the Institute of Medicine’s standards for developing trustworthy clinical guidance documents. To conduct independent and objective systematic reviews of the literature, SNMMI has contracted with the Oregon Health and Science University’s Evidence-based Practice Center. The primary purpose of these systematic reviews is to assess the literature for evidence describing the diagnostic accuracy and comparative effectiveness of selected nuclear medicine procedures in clinical decision making and patient outcomes.

One of the high-value topics on which AUC are currently under development is PET Myocardial Perfusion Imaging. This endeavor is being led by Thomas H. Schindler, MD, PhD, with Washington University of St. Louis. It is a true multidisciplinary effort with official representation from several relevant specialty societies. In addition to the representatives from SNMMI, the expert panel for this AUC workgroup includes nominees from one of the College of Cardiology, the American Society of Nuclear Cardiology, the European Association of Nuclear Medicine, the American College of Nuclear Medicine, and the American College of Physicians. The expert panel has identified more than 260 clinical scenarios for PET MPI and is currently in the process of finalizing the appropriateness scores for these indications. The anticipated completion for this AUC is the first quarter of 2019. More information on the society’s AUC efforts can be found at www.snmmi.org/AUC.

References:
1. PAMA: https://www.cms.gov/Medicare/Medicare-Fee-for-Ser- vice-Payment/LogicalLabFeeSched/PAMA-regulations.html.

Theranostics Consensus Conference in Anaheim page 7.

The clinical trials for this early stage will require the identification of new study endpoints—perhaps an imaging endpoint. Lastly, as a field, we must ensure that we have the workforce that is adequately trained in the use of radionuclide therapies.

A summary paper will be published, and sessions from the conference were recorded and will be made available for members to view online. This important discussion will continue during a categorical at the SNMMI 2019 Annual Meeting in Anaheim, CA (June 22-25).

We would like to recognize Daniel Pryma, MD (president of the SNMMI Therapy Center of Excellence), Daniel Lee, MD (vice president of the SNMMI Therapy Center of Excellence), and John Sunderland, PhD, MBA (Clinical Trials Network co-chair), as the organizers of this initial consensus conference. Additionally, we wish to thank FDA and NCI for their commitment and dedication to the conference; their participation in formal talks and hallway conversations were valued by the attendees. Thank you for your hard work in leading this cutting-edge space of research and medicine.

The slides from the conference will soon be available on the CTN website: www.snmmi.org/ctn
Connect The Pieces and Initiate Your Site’s Compliance Strategy

Are Your PET/CT Scanners Joint Commission Compliant?
The Joint Commission recently updated the diagnostic imaging requirements for the hospital and ambulatory care programs.

SNMMI will analyze your images and send you back a report signed by a qualified physicist documenting compliance with the new Joint Commission diagnostic imaging requirements.

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ctnadmin@snmmi.org

Save the Dates

SNMMI 2019 Mid-Winter Meeting
January 17–19, 2019 • Palm Springs, CA

5th Theraonotics World Congress 2019
March 1–3, 2019 • Jeju-do, Korea

40th Annual High-Country Nuclear Medicine Conference
March 2–6, 2019 • Vail, CO

ASNC Nuclear Cardiology Today 2019
April 12–14, 2019 • Tampa, FL

ASCO Annual Meeting 2019
May 31–June 4, 2019 • Chicago, IL

SNMMI 2019 Annual Meeting
June 22–25, 2019 • Anaheim, CA

DIA Annual Meeting 2019
June 23–27, 2019 • San Diego, CA

WMIC 2019—World Molecular Imaging Congress
September 4–7, 2019 • Montreal, Quebec

European Association of Nuclear Medicine (EANM19)
October 12–16, 2019 • Barcelona, Spain

RSNA 105th Scientific Assembly and Annual Meeting
December 1–5, 2019 • Chicago, IL

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