Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofCardiovascularCT.com

Clinical Trial Design

Regadenoson-stress myocardial CT perfusion and single-photon emission CT: Rationale, design, and acquisition methods of a prospective, multicenter, multivendor comparison

Ricardo C. Cury MD[a,*], *Therese M. Kitt MD*[b], *Kathleen Feaheny MS*[c], *Jamie Akin MSHS*[c], *Richard T. George MD*[d]

[a] *Baptist Hospital of Miami and Baptist Cardiac and Vascular Institute, 8900 North Kendall Dr, Miami, FL 33176, USA*
[b] *Astellas Scientific and Medical Affairs, Inc., Northbrook, IL, USA*
[c] *Astellas Pharma Global Development, Inc., Northbrook, IL, USA*
[d] *Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA*

ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form
29 August 2013
Accepted 3 September 2013
Available online 5 December 2013

Keywords:
Regadenoson
Cardiovascular imaging
Pharmacologic stress
CT perfusion imaging
Single-photon emission CT
Study design

ABSTRACT

Pharmacologic stress myocardial CT perfusion (CTP) has been reported to be a viable imaging modality for detection of myocardial ischemia compared with single-photon emission CT (SPECT) in several single-center studies. However, regadenoson-stress CTP has not previously been compared with SPECT in a multicenter, multivendor study. The rationale and design of a phase 2, randomized, cross-over study of regadenoson-stress myocardial perfusion imaging by CTP compared with SPECT are described herein. The study will be conducted at approximately 25 sites by using 6 different CT scanner models, including 64-, 128-, 256-, and 320-slice systems. Subjects with known/suspected coronary artery disease will be randomly assigned to 1 of 2 imaging procedure sequences; rest and regadenoson-stress SPECT on day 1, then regadenoson-stress CTP and rest CTP/coronary CT angiography (same acquisition) on day 2; or regadenoson-stress CTP and rest CTP/CT angiography on day 1, then rest and regadenoson-stress SPECT on day 2. The prespecified primary analysis examines the agreement rate between CTP and SPECT for detecting or excluding ischemia ($\geq$2 or 0–1 reversible defects, respectively), as assessed by 3 independent blinded readers for each modality. Non-inferiority will be indicated if the lower boundary of the 95% CI for the agreement rate is within 0.15 of 0.78 (the observed agreement rate in the regadenoson pivotal trials). The protocol described herein will support the first evaluation of regadenoson-stress CTP by using multiple scanner types compared with SPECT.

This clinical trial is registered at www.clinicaltrials.gov as NCT01334918.

Conflict of interest: R.C.C. has received consulting fees/honoraria from Astellas Pharma and has received grants from Astellas and GE Healthcare. T.M.K., K.F., and J.A. are employees of Astellas Pharma. R.T.G. has received consulting fees/honoraria from ICON Medical Imaging; has served on advisory boards for GE Healthcare; has received research grants from Toshiba and GE Healthcare and educational grants from Toshiba. Medical writing support was provided by Emily Hutchinson of Envision Scientific Solutions, funded by Astellas Scientific and Medical Affairs, Inc.

* Corresponding author.
E-mail address: rcury@baptisthealth.net (R.C. Cury).

1934-5925/$ – see front matter
http://dx.doi.org/10.1016/j.jcct.2013.09.004

1. Introduction

Detection of coronary artery disease (CAD)-associated myocardial ischemia is of paramount importance for guiding therapy and for determining the best revascularization strategies. As such, myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is an integral part of cardiology practice. Visualization of myocardial ischemia by SPECT is based on the distribution of radiopharmaceutical agents, corresponding to coronary blood flow. Reversible and fixed myocardial perfusion defects are identified by SPECT scans performed at rest and under conditions of increased coronary blood flow or "stress"; reversible defects are observed only under stress conditions, whereas fixed defects can also be observed at rest.[1,2]

Increased coronary blood flow can be brought about by exercise or pharmacologic stress. Pharmacologic stress is indicated in patients unable to undergo an adequate exercise test because of noncardiac physical limitations or patients with baseline electrocardiogram (ECG) abnormalities.[3] The pharmacologic stress agents adenosine and regadenoson are adenosine receptor agonists, with coronary vasodilation primarily mediated by the A_{2A} receptor.[4] Although adenosine is an agonist of multiple adenosine receptor subtypes, regadenoson is selective for the adenosine A_{2A} receptor.[5,6]

Several studies have reported the diagnostic accuracy of coronary CT angiography (CTA) to detect or exclude CAD.[7–9] Although considered an effective tool for excluding CAD in patients at low-to-intermediate risk, the use of CTA without corresponding perfusion data in patients at moderate-to-high risk of CAD remains controversial. CTA provides anatomic information, and, because the presence of coronary stenosis does not necessarily imply the presence of myocardial ischemia, there is the potential for overestimation of disease and false-positive results in the presence of dense calcified plaques and preexisting stents.[10,11]

Combined assessment of coronary anatomy and myocardial perfusion by using CTA and stress CT perfusion (CTP) would provide both anatomic and functional data.[11] Recent studies have shown that adenosine-stress perfusion as assessed by CTP is feasible, with results comparable with SPECT MPI for the detection of perfusion abnormalities.[12–15] However, regadenoson-stress CTP has not previously been compared with SPECT in a multicenter, multivendor study.

We describe here the rationale, design, and CTP methods of the first study to compare regadenoson-stress CTP and SPECT for visualization of myocardial ischemia.

2. Methods

2.1. Objective

The primary objective of this article is to report the study design for a phase 2, multicenter, multivendor, open-label, randomized, cross-over clinical trial (registered at www.clinicaltrials.gov as NCT01334918) to assess the non-inferiority of regadenoson-stress CTP with regadenoson-stress SPECT in detecting the presence or absence of myocardial ischemia.

2.2. Study overview

The study will enroll subjects at approximately 25 centers in the United States. Sites will be selected to participate on the basis of peer recommendations and having a minimum of 2 years prior CT imaging experience. The study protocol and a manual of image acquisition operating procedures will be made available to all CT technologists and primary investigators. On-site, protocol-specific training will be provided, and all CT technologists and primary investigators will be required to demonstrate competency with 100% accuracy via open-book examination. CT technologists will be required to perform the entire protocol successfully with the use of a phantom. Sites will be required to pass a quality check without protocol deviations before they will be allowed to enroll additional subjects to the trial.

On study day 1, subjects will be randomly assigned to 1 of 2 imaging procedure sequences (Fig. 1). Subjects allocated to imaging procedure sequence 1 will have a rest SPECT scan followed by a regadenoson-stress SPECT scan on day 1, then a regadenoson-stress CTP scan and a rest CTP (and CTA, same acquisition) scan on day 2. Subjects allocated to imaging procedure sequence 2 will have a regadenoson-stress CTP scan and a rest CTP (and CTA) scan on day 1, then a rest SPECT scan and a regadenoson-stress SPECT scan on day 2. Subjects will be randomly assigned to the different imaging sequences because regadenoson-related side effects may be more apparent to the subject the first time it is administered, compared with subsequent administrations. This approach will also help to identify adverse events that are a result of the testing procedure itself.

After completion of all 4 scans, each final image will be assessed at a central laboratory by 3 independent blinded readers for each modality.

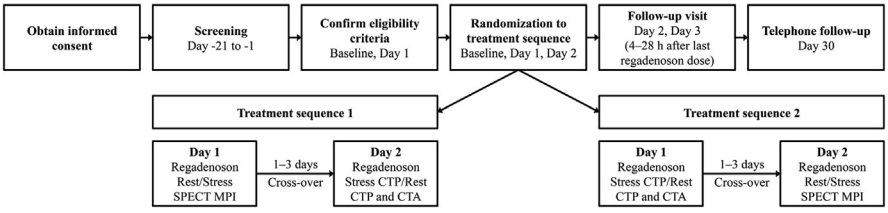

Fig. 1 – Overview of study enrollment, randomization, and follow-up events. CTA, CT angiography; CTP, CT perfusion; MPI, myocardial perfusion imaging; SPECT, single-photon emission CT.