Off-label, but on-target: Use of regadenoson with exercise

Robert C. Hendel, MD and Lauren Frost, MD

See related article, pp. 185–196

Pharmacologic stress testing has evolved considerably during the past 25 years, providing an extension of the benefits of physiologic imaging to those who are unable to undergo maximal exercise testing. Vasodilator stress myocardial perfusion imaging now compromises more than half of nuclear cardiology procedures in the United States,[1] as multiple procedural advances and additional clinical evidence support this procedure as a mainstay in cardiac testing.

The clinical use of pharmacologic testing began with oral and intravenous dipyridamole and later with intravenous adenosine, which provided a more reliable hyperemic response with regards to coronary blood flow, a short half-life, and an outstanding safety profile. More recently, we have seen the introduction of selective A2a agonists, with regadenoson presently available for clinical use. This agent offers not only the potential for an improved side effect profile but also a unique dosing strategy.[2] With a fixed dose administration via an intravenous bolus, regadenoson may be administered easily and rapidly at any give time, even when patients are actively exercising on a treadmill or bicycle. The need for terminating the exercise protocol, drawing up the appropriate weight-based dose, and preparing the infusion pump is obviated; regadenoson may be administered ''on demand'' while the patient is still performing exercise.

Why is the adjunctive use of exercise with vasodilator stress important? Multiple publications with dipyridamole and adenosine have clearly demonstrated improved image quality, reduced bothersome side effects such as flushing and abdominal discomfort, and enhanced safety, mostly due to reduced conduction disturbances.[3-7] Regadenoson has now been in clinical use for approximately 5 years and virtually from its day of approval, laboratories have been using adjunctive exercise with this agent to improve side effect profile and image quality. Yet, to date, only limited data has been published using combined exercise and regadenoson stress; none of these trials have been multicenter in nature and few have had the rigor of a pivotal clinical trial, such as ADVANCE MPI.[2] However, image quality, safety, and adverse effects are all favorably impacted by the additional of exercise with regadenoson administration.[8-10]

In this issue of the Journal, Parker et al report the findings of a randomized trial comparing dipyridamole with exercise to regadenoson with exercise.[11] This study is unique in that the administration of the vasodilator was ''conditional'' and not necessarily administered to all patients who were exercising. The results demonstrate that half of the patients did not require regadenoson administration, thereby reducing potential side effects and cost. This study also confirmed the benefits of adjunctive exercise, impacting on image quality, safety, and adverse effects.

If exercise is so beneficial for most patients undergoing vasodilator stress, why is this not part of promotion materials that accompany regadenoson? The unfortunate reality is that combining exercise with regadenoson is considered an ''off-label'' use of this agent, designed for pharmacologic stress testing in patients ''unable to undergo adequate exercise stress''.[12] In the past 3 years, more than $9 billion in penalties have been levied against pharmaceutical manufactures for the marketing of off-label use of prescription medications.[13] Regadenoson's manufacturer (Astellas Pharma US, Inc) has therefore been appropriately concerned about promoting an off-label use of this agent. Although there may be a theoretical risk of reduced safety, unacceptable side effects, or a change in the diagnostic accuracy when exercise is added to vasodilator stress imaging, there is no evidence for such concern. However, rigorous trial data, such as with a phase 3 study, are lacking. To provide such pivotal clinical data to support off-label medication use, such as the when combining regadenoson with exercise, is exorbinently expensive and time consuming, often exceeding the potential supplemental revenue.[14]

From the Cardiovascular Division, University of Miami Miller School of Medicine, Miami, FL.

Reprint requests: Robert C. Hendel, MD, Cardiovascular Division, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 1123, CRB, Miami, FL 33136; *rhendel@med.miami.edu*.

J Nucl Cardiol 2013;20:179–81.
1071-3581/$34.00

doi:10.1007/s12350-012-9643-5

This discussion is germane in the context of the current paper as the use of regadenoson, when added on a ''conditional'' basis, as proposed by Parker et al, is ''off-label''. When examining the indications for adenosine or regadenoson, these agents do not allow for use except in patients who are unable to undergo adequate exercise. In fact, adenosine use with Tc-99m sestamibi or Tc-99m tetrofosmin is an off-label use, as this agent is only indicated for use with thallium-201.[15]

Should we only use medications ''on-label'' indications? It has been estimated that 21% of prescriptions are written for an off-label use.[16] Certainly few question the common wisdom of using beta blockers in heart failure—despite the lack of an FDA-approved indication for such practice. Clinicians have rightly adopted off-label use of medications when clinical evidence was present to firmly support these applications. In fact, such off-label use may become widespread and the predominant approach to certain conditions. The FDA actually supports this approach as the Agency does not wish to control the practice of medicine but states that physicians have the ''responsibility to be well informed about the product (and) to base its use on firm scientific rationale and sound medical evidence''.[17] Such appears to be the situation with the use of exercise with vasodilator stress, given the multiple published reports of improvements in diagnostic accuracy, safety, side effects, and image quality.

An interesting issue relates to the marketing and promotion of the off-label use of mediations, which is not permitted. However, following a 2009 ruling, the manufacturer is explicitly permitted to disseminate published peer reviewed articles in their entirety that describe unapproved uses and may do so without seeking special permission.[18] This is a worthwhile first step and the combined exercise and vasodilator stress papers should be widely distributed to promote optimal practice. Another approach would mandate fundamental changes within FDA and other regulatory bodies, and include ''a better process (which) would allow an easier updating of indication labeling that is concordant and commensurate with the strength of the evidence.''[19]

The current trial by Parker et al reinforces the use of exercise testing with vasodilator stress as optimal practice, even though it is considered ''off-label'' use. The authors extend the process of testing, however, to use regadenoson only when necessary, taking advantage of the simple logistics related to its administration. This publication suggests, appropriately, that we should exercise most of our patients in the stress lab and inject pharmacologic stress agents only when needed. However, even when regadenoson is administered, the use of adjunctive exercise is highly beneficial. Parker et al champion an innovative hybrid approach that optimizes stress testing using a technique of exercise and pharmacologic stress, a practice that is off-label, but certainly on-target.

References

1. 2012 AMR/Arlington Medical Resources, LLC All rights reserved. Reproduction, distribution, transmission or publication is prohibited. Reprinted with permission.
2. Iskandrian AE. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: Results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007;14:645-58.
3. Holly TA, Satran A, Bromet DS, et al. The impact of adjunctive adenosine infusion during exercise myocardial perfusion imaging: Results of the both exercise and adenosine stress test (BEAST) trial. J Nucl Cardiol 2003;10:291-6.
4. Elliott MD, Holly TA, Leonard SM, Hendel RC. Impact of an abbreviated adenosine protocol incorporating adjunctive treadmill exercise on adverse effects and image quality in patients undergoing stress myocardial perfusion imaging. J Nucl Cardiol 2000;7:584-9.
5. Jamil G, Ahlberg AQ, Eliott MD, et al. Impact of limited treadmill exercise on adenosine Tc-99m sestambi single-photon emission computed tomographic myocardial perfusion imaging in coronary artery disease. Am J Cardiol 1999;84:400-3.
6. Thomas GS, Prill NV, Majmundar H, et al. Treadmill exercise during adenosine infusion is safe, results in fewer adverse reactions and improves myocardial perfusion imaging. J Nucl Cardiol 2000;7:439-46.
7. Vitola JV, Brambatti JC, Caligaris F, et al. Exercise supplementation to dipyridamole prevents hypotension, improves electrocardiogram sensitivity, and increases heart-to-liver activity ratio on Tc-99m sestamibi imaging. J Nucl Cardiol 2001;8:652-9.
8. Thomas GS, Thompson RC, Miyamato MI, et al. The regEx trial: A randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A(2A) adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. J Nucl Cardiol 2009;16:63-72.
9. Kwon DH, Cerqueira MD, young R, et al. Lessons from regadenason and low-level treadmill/regadenason myocardial perfusion imaging: Initial clinical experience in 1263 patients. J Nucl Cardiol 2010;17:853-7.
10. Partington SL, Lanka V, Hainer J, et al. Safety and feasibility of regadenoson use for suboptimal heart rate response during symptom-limited standard Bruce exercise stress test. J Nucl Cardiol 2012;19:970-8.
11. Parker MW, Morales DC, Slim HB, et al. A strategy of symptom-limited exercise with regadenoson-as-needed for stress myocardial perfusion imaging: a randomized controlled trial. J Nucl Cardiol 2012. doi:10.1007/s12350-012-9641-7.
12. Regadenoson[package insert]. Northbrook, IL: AstellasPharma US, Inc; Revised 2012 July.
13. Wittich CM, Burkle C, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc 2012;87:982-90.
14. Stafford PS. Regulating off-label drug use: Rethinking the role of the FDA. N Engl J Med 2008;358:1427-9.
15. PI Adenosine [package insert]. Northbrook, IL: AstellasPharma US, Inc; Revised 2012 July.

16. Radley DC, Findelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med 2006;166:1021-6.
17. Food and Drug Administration (FDA). ''Off label'' and investigational use of marketed drugs, biologics, and medical devices. http://www.fda.gov/oc.ohrt/irbs/offlabel.html. Accessed 29 Sept 2012.
18. Mello MM, Studdert DM, Brennan TA. Shifting terrain in the regulation of off-label promotion of pharmaceuticals. N Engl J Med 2009;360:1557-66.
19. O'Malley PG. What does off-label prescribing really mean? Arch Intern Med 2012;172:759-60.