CORRESPONDENCE

Riociguat for Pulmonary Hypertension

TO THE EDITOR: With regard to the articles on the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (CHEST-1) and the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) by Ghofrani et al. (July 25 issue)[1,2] and the corresponding editorial by Archer,[3] we agree that pharmacotherapy should be available to patients with inoperable disease. However, the observed improvements in exercise capacity with riociguat for chronic thromboembolic pulmonary hypertension are inferior in magnitude, and their durability is unknown, as compared with reported outcomes after surgery, which is associated with an approximate 2% mortality and is curative in many patients.[4] The importance of establishing operability in patients with chronic thromboembolic pulmonary hypertension is paramount before the initiation of medical therapy, and the definition of operability should be determined at experienced surgical centers. Our center has performed roughly 3000 operations, and many of our patients have had distal or segmental obstruction, high levels of pulmonary vascular resistance, or both and so have been deemed to have inoperable disease at some centers, but these patients have had excellent outcomes with interventions performed by experienced surgeons. Furthermore, medical therapy in chronic thromboembolic pulmonary hypertension may delay the operation unnecessarily and make removal of the organized thrombus more difficult.[5] Accordingly, we emphasize caution with the use of temporizing therapies for a disease for which more definitive approaches are viable.

William R. Auger, M.D.
Stuart W. Jamieson, M.B.
University of California San Diego Health System
La Jolla, CA
bauger@ucsd.edu
for the Pulmonary Thromboendarterectomy Program at University of California, San Diego

No potential conflict of interest relevant to this letter was reported.

1. Ghofrani H-A, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369:319-29.
2. Ghofrani H-A, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369:330-40.
3. Archer SL. Riociguat for pulmonary hypertension — a glass half full. N Engl J Med 2013;369:386-8.
4. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. Ann Thorac Surg 2012;94:97-103.
5. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. Circulation 2009;120:1248-54.

DOI: 10.1056/NEJMc1312903

TO THE EDITOR: The oral soluble guanylate cyclase stimulator riociguat may increase the sensitivity of soluble guanylate cyclase to endogenous nitric oxide, resulting in increased production of its intracellular second messenger, cyclic guanosine monophosphate (cGMP). Evidence suggests that enhanced activation of the cGMP pathway may lead to cGMP-dependent protein kinase 1–mediated phosphorylation of phosphodiesterase-5 and to an increase in phosphodiesterase-5 activity.[1] Activation of phosphodiesterase-5, in turn, may enhance cGMP hydrolysis, limiting the amplitude and duration of a cGMP signal and consequently the effect of riociguat.[1] This observation suggests that the use of a combination of riociguat plus a

THIS WEEK'S LETTERS

phosphodiesterase-5 inhibitor such as sildenafil, as compared with the use of either agent alone, may improve outcomes.

Emmanuel E. Egom, M.D., Ph.D.
Dalhousie University
Halifax, NS, Canada
eeegom@dal.ca

No potential conflict of interest relevant to this letter was reported.

1. Mullershausen F, Friebe A, Feil R, Thompson WJ, Hofmann F, Koesling D. Direct activation of PDE5 by cGMP: long-term effects within NO/cGMP signaling. J Cell Biol 2003;160:719-27.

DOI: 10.1056/NEJMc1312903

TO THE EDITOR: The CHEST-1 investigators showed that riociguat significantly improved exercise capacity and pulmonary vascular resistance in patients with chronic thromboembolic pulmonary hypertension. According to the 2011 guidelines for the treatment of chronic thromboembolic pulmonary hypertension, patients with this condition should receive lifelong anticoagulation, usually with doses of vitamin K antagonists adjusted to a target international normalized ratio between 2.0 and 3.0.[1] However, there is no mention of the current anticoagulation status of the patients with chronic thromboembolic pulmonary hypertension in CHEST-1. Anticoagulation therapy could be an important confounding factor for the efficacy analysis, especially in patients with inoperable chronic thromboembolic pulmonary hypertension. In the simultaneously published article on PATENT-1, a subgroup analysis showed that the functional benefits of riociguat therapy tended to be greater in patients who had received prostanoids; this finding was also mentioned in the accompanying editorial. Although patients in CHEST-1 were excluded if they had received concomitant medical therapy, previous medical therapy should be considered as a factor in that analysis.

Jaewon Oh, M.D.
Jong-Chan Youn, M.D., Ph.D.
Seok-Min Kang, M.D., Ph.D.
Yonsei University College of Medicine
Seoul, South Korea
smkang@yuhs.ac

No potential conflict of interest relevant to this letter was reported.

1. Wilkens H, Lang I, Behr J, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011;154:Suppl 1:S54-S60.

DOI: 10.1056/NEJMc1312903

TO THE EDITOR: In their article on riociguat for the treatment of pulmonary arterial hypertension, Ghofrani et al. report the inclusion of 221 of 443 symptomatic patients with pulmonary arterial hypertension (50%) who were not receiving background therapy. According to the guidelines of the European Society of Cardiology and the European Respiratory Society for the treatment of pulmonary hypertension, published in 2009, all patients who are in World Health Organization (WHO) functional class II to IV should receive targeted therapy for pulmonary arterial hypertension (the recommendation is class I, level of evidence A).[1] A total of 22% of patients were in WHO functional class III or IV without appropriate treatment for pulmonary arterial hypertension before inclusion in the current study; these patients had a significant decrease in the 6-minute walk distance (–37 m) after receiving placebo for 12 weeks. A meta-analysis of clinical trials involving patients with pulmonary arterial hypertension, including 3140 symptomatic patients, showed a 43% reduction in mortality in the active-treatment groups as compared with the placebo groups during an average of 14 weeks.[2] Data are lacking regarding head-to-head risks and benefits of established effective agents so that clinicians and patients may make informed clinical decisions.[3] Furthermore, it seems to be unethical to perform placebo-controlled trials involving symptomatic patients with pulmonary arterial hypertension who have not received targeted therapy for pulmonary arterial hypertension and who are at increased risk for death with placebo.

Martijn C. Post, M.D., Ph.D.
St. Antonius Hospital
Nieuwegein, the Netherlands
m.post@antoniusziekenhuis.nl

Dr. Post reports receiving lecture fees from Actelion and Pfizer and speaking fees from Actelion, Pfizer, and Bayer. No other potential conflict of interest relevant to this letter was reported.

1. The Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology, European Respiratory Society. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-63.
2. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403.
3. Pearson SD. Placebo-controlled trials, ethics, and the goals of comparative effectiveness research: comment on "lack of head-to-head trials and fair control arms." Arch Intern Med 2012;172:244-5.

DOI: 10.1056/NEJMc1312903

THE AUTHORS REPLY: Auger and Jamieson highlight the importance of pulmonary endarterectomy as a potentially curative treatment for chronic thromboembolic pulmonary hypertension. In CHEST-1, rigorous measures were taken to ensure that only patients with chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable or who had persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were included. An expert committee to assess operability reviewed 51% of cases during screening; local decisions (by a collaborating experienced surgeon, as defined in the study protocol) were permitted in the remaining 49% of cases. We completely agree that the availability of a new specific medication for patients with inoperable chronic thromboembolic pulmonary hypertension should not exclude any patient from this potentially curative surgical therapy.

In response to Egom: direct soluble guanylate cyclase stimulation by riociguat leads to dose-dependent production of cGMP and vasodilatory effects that cannot be further maximized by coadministration of a phosphodiesterase-5 inhibitor.[1] This is the rationale for individual dose adjustment of riociguat (according to a strict protocol) that is limited by the predefined boundaries of systemic systolic blood pressure. Although concomitant administration of a phosphodiesterase-5 inhibitor could in theory result in increased efficacy, this would most likely occur only in patients receiving an insufficient dose of riociguat, which in clinical practice should not happen. Furthermore, PATENT PLUS (Evaluation of the Pharmacodynamic Effect of the Combination of Sildenafil and Riociguat on Blood Pressure and Other Safety Parameters) showed no evidence of a positive risk–benefit assessment when riociguat was combined with a standard dose of sildenafil, predominantly because of the number of discontinuations,[2] and this combination is contraindicated in the prescribing information for riociguat in the United States and Canada.

Oh et al. note that lifelong anticoagulation is mandatory in patients with chronic thromboembolic pulmonary hypertension. All patients received effective oral anticoagulation for 3 months or more before enrollment and throughout CHEST-1, as stipulated in the study protocol.

Finally, the concerns raised by Post were seriously considered when the study was designed in 2006 and 2007. All local ethics committees approved the study, and all patients were informed about the potential risks and benefits of participating. Given the relatively short duration of the study, the fact that predefined criteria for discontinuation were implemented to allow patients to switch to commercially available therapy for pulmonary arterial hypertension if needed, and that medications specifically for pulmonary arterial hypertension are not available in all countries, it was considered justifiable to conduct the study in this way.

Hossein-Ardeschir Ghofrani, M.D.
Universities of Giessen and Marburg Lung Center
Giessen, Germany
ardeschir.ghofrani@innere.med.uni-giessen.de

Gerald Simonneau, M.D.
Université Paris-Sud
Le Kremlin–Bicêtre, France

Lewis J. Rubin, M.D.
University of California, San Diego
La Jolla, CA

for the Authors of CHEST-1 and PATENT-1

Since publication of their articles, the authors report no further potential conflict of interest.

1. Schermuly RT, Janssen W, Weissmann N, Stasch J-P, Grimminger F, Ghofrani H-A. Riociguat for the treatment of pulmonary hypertension. Expert Opin Investig Drugs 2011;20:567-76.
2. Galiè N, Neuser D, Müller K, at el. A placebo-controlled, double-blind phase II interaction study to evaluate blood pressure following addition of riociguat to patients with symptomatic pulmonary arterial hypertension (PAH) receiving sildenafil (PATENT PLUS). Am J Respir Crit Care Med 2013;187: Suppl:A3530. abstract.

DOI: 10.1056/NEJMc1312903

Randomized Clinical Trials — Removing Obstacles

TO THE EDITOR: Reith et al. (Sept. 12 issue)[1] suggest that clinical trials comparing widely accepted therapies should not be held to the "excessively detailed informed consent" standards of trials involving new therapies. Their justification appears to be as follows: for treatment purposes, patients already accept the risks of well-understood therapies for which evaluative data are