CLINICAL IMAGE

Roxadustat: another drug that causes pulmonary hypertension? Report of first human case

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Roxadustat (INN, FG-4592) is a first-in-class oral drug for treating anemia in chronic kidney disease. It is a second-generation hypoxia-inducible factor (HIF) prolyl-hydroxylase-2 (PHD2) inhibitor.[1] The drug proved effective in recent clinical trials (phase III OLYMPUS and ROCKIES trials for roxadustat met their primary endpoints in chronic kidney disease patients with anemia) and was recently granted market approval in China. We present a patient who developed severe pulmonary arterial hypertension (PAH) while being treated in a phase III clinical trial of roxadustat. Such an association has never been described for a PHD2 inhibitor before. HIF-α hydroxylase system is involved in the regulation of vascular remodeling.

A 74-year-old woman was hospitalized due to sudden unexplained worsening of exercise tolerance and shortness of breath. Her medical history included stable chronic angina (remote myocardial infarction without detectable left ventricular dysfunction), hypothyroidism, and diabetes. In May 2016, she was recruited for phase III trial with oral roxadustat in adjusted doses of 40 to 100 mg 3 times a week because of her stage G4 chronic kidney disease with anemia. The trial lasted 24 months. After that she was admitted to our department with class III heart failure with the 6-minute walk test distance of 100 m. An electrocardiogram showed sinus rhythm at 70 bpm with flat negative T waves in all leads. Laboratory tests on admission showed a glomerular filtration rate of 20.5 ml/min/1.73 m^2, hemoglobin level of 10.6 g/dl, and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) level of 14 596 pg/ml. Echocardiography showed enlargement of the right cavities of the heart, features of PAH with depressed right ventricular systolic function (estimated systolic pulmonary artery pressure [PAP], 87 mm Hg; mean PAP, 47 mm Hg; diastolic PAP, 24 mm Hg), and moderate tricuspid regurgitation, whereas left ventricular ejection fraction was normal at 56% (FIGURE 1). Pulmonary hypertension was

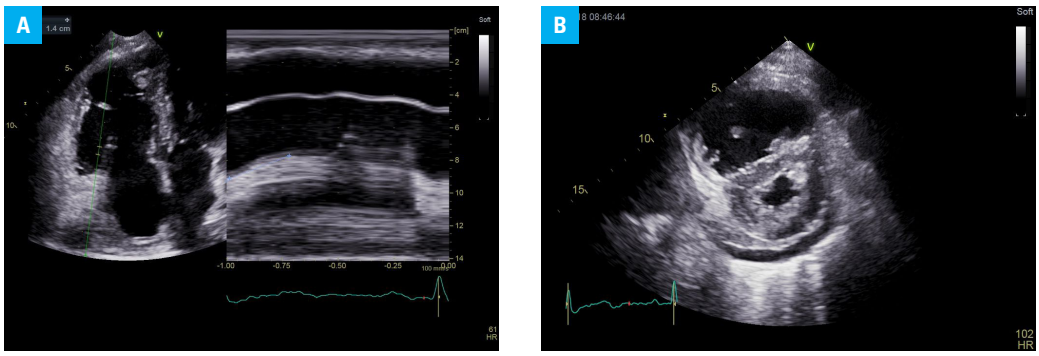

FIGURE 1 Transthoracic echocardiography and electrocardiography imaging: **A** – measurement of the tricuspid annular plane systolic excursion using M-mode echocardiography; the value of 14 mm shows a significant impairment of the contractility of the right ventricular free wall. **B** – enlargement of the right ventricle with systolic flattening of the intraventricular septum and small posterior pericardial effusion are shown on the parasternal short axis projection.

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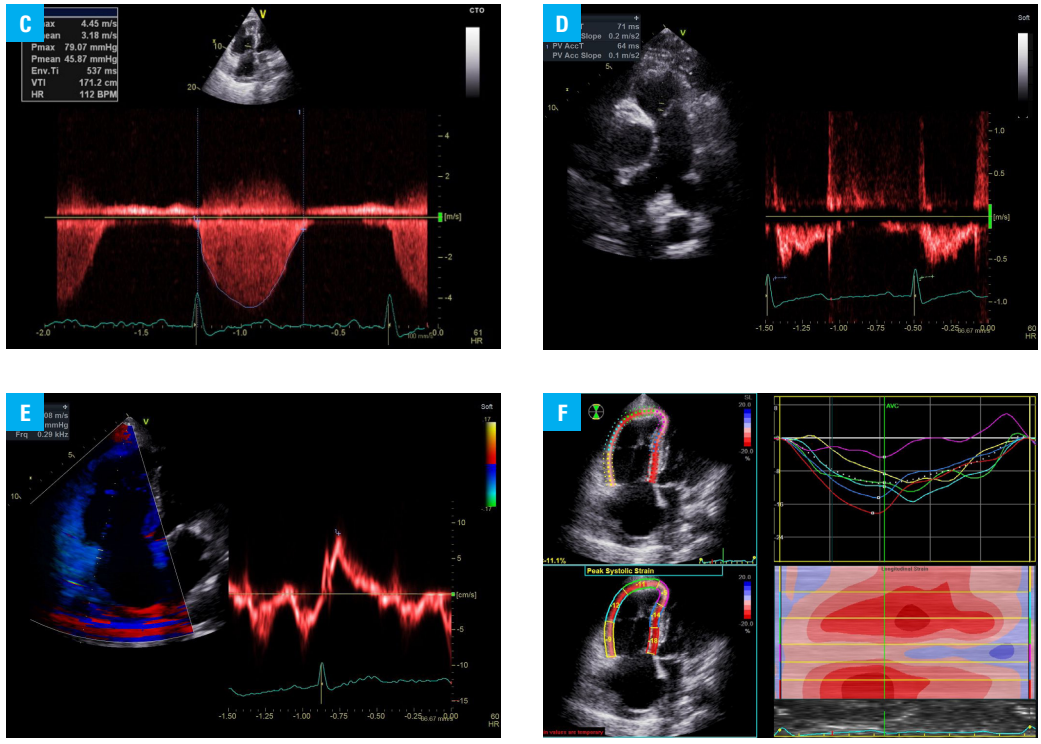

FIGURE 1 Transthoracic echocardiography and electrocardiography imaging: **C** – continuous--wave spectral Doppler of the tricuspid valve; maximum velocity of 4.45 m/s corresponds with right ventricular–right atrial gradient of 79 mm Hg. **D** – pulsed--wave Doppler interrogation of the right ventricular outflow tract with short ejection acceleration time (71 ms), which suggests pulmonary hypertension with the mean pulmonary artery pressure of 47 mm Hg; **E** – longitudinal velocity of the tricuspid annulus measured with tissue Doppler echocardiography is reduced to 8 cm/s. **F** – calculation of right ventricular strain from a modified apical 4-chamber view demonstrating a severely abnormal value for free wall segments (–11% averaged for 3 segments of the right ventricular free wall; normal value, less than –25%)

not suspected on echocardiography performed in June 2012. Right heart catheterization confirmed irreversible precapillary PAH (mean PAP, 48 mm Hg, pulmonary vascular resistance, 12.3 WU). Pulmonary embolism was excluded.

The treatment of PAH was initiated with oral sildenafil (20 mg 3 times a day), and subcutaneous treprostinil, escalated to a current dose of 42.5 ng/kg/min along with escalation of loop diuretics. As roxadustat was considered a potential contributor to the development of PAH, it was discontinued (May 2018) and replaced with erythropoietin. On the last follow-up on November 19, 2018, after 5 months of PAH-specific treatment, the 6-minute walk test distance was 200 m, NT-proBNP was 1385 pg/ml, and hemoglobin level was 11.2 g/dl. Echocardiographic parameters also improved. Thus, functional improvement was seen even though anemia worsened after withdrawal of roxadustat.

To our best knowledge, this report is probably the first to document the development of severe PAH during roxadustat therapy for anemia. The drug inhibits PHD2, an enzyme responsible for breaking down HIF under normoxic conditions. Stabilization of HIF2α upregulates *Notch3* and transforming growth factor β, as well as increases the pericyte coverage and transformation of pericyte into myofibroblasts or vascular smooth muscle cells, which is associated with remodeling of pulmonary arterioles and PAH development.[2] Inhibition (or gene knockout) of PHD2 increases the HIF2α level and enhances endothelial-to-mesenchymal transition with upregulation of *SNAI1/2* genes in the lung. Thus, the HIF pathway is linked with adverse vascular remodeling and experimentally confirmed to induce PAH.[3] Roxadustat's mode of action is related to erythropoietin, which was shown to stimulate proliferation of endothelial and smooth muscle cells in pulmonary vasculature.[4]

We understand that our report cannot prove a causal relationship between roxadustat and development of PAH; however, it is plausible that the mode of action of roxadustat is linked to the pathophysiology of PAH.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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