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Twelve-Year Survival in a Patient With Systemic Sclerosis–Associated Pulmonary Arterial Hypertension on Nifedipine Monotherapy

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Abstract

Pulmonary arterial hypertension is a progressive vascular disease with a high mortality rate without proper therapy. Identification of the appropriate treatment for each patient is critical in regard to adverse effects, health care costs, ease of treatment, and the potential for prognostication. Treatment strategies typically begin with acute vasoreactivity testing, which is performed during a right heart catherization. If positive, a calcium channel blocker may work; however, another pulmonary arterial hypertension–specific medication is necessary when testing is negative. Acute vasoreactivity testing is currently recommended to be performed only in certain subgroups of pulmonary arterial hypertension, but not when related to connective tissue disease. In this report, we describe a patient who had systemic sclerosis–related pulmonary arterial hypertension with a positive acute vasoreactivity test result. The patient was placed on calcium channel blocker monotherapy that has been well tolerated for 12 years, resulting in improved symptoms and exercise capacity. The long-term response to calcium channel blocker therapy in systemic sclerosis–associated pulmonary arterial hypertension has not been previously described. In addition, pulmonary artery pressures have been well controlled. The absence of genetic smooth muscle variants prevalent in vasoresponsive idiopathic pulmonary arterial hypertension is also unique.

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BACKGROUND

The treatment of pulmonary arterial hypertension (PAH) has multiple options that vary widely in cost, adverse effects, and effectiveness. Initial therapy selection is based on the patient's pulmonary arterial vasoreactivity. Acute vasoreactivity testing (AVT) is performed in patients with certain subsets of PAH to determine whether a calcium channel blocker (CCB) may be used for treatment. In the current guidelines, AVT is only recommended in patients with idiopathic, heritable, and drug-associated PAH.[1] These recommendations are based on the lack of evidence for treating other subgroups of PAH with CCBs despite being among the least expensive, safest, and best tolerated of the PAH medications. The current evidence shows that patients with a positive AVT result and treatment with a CCB have 10–year survival greater than 90% in patients with idiopathic PAH.[2]

Patients with nonidiopathic PAH, such as those with systemic sclerosis (SSc)-associated PAH, may have a positive AVT result but a poor response to CCB therapy.[3-5] In a study performed more than 20 years ago, patients with SSc and CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) with PAH were successfully treated with a CCB.[6] Because of this variation in response to AVT and CCB therapy, recent studies have focused on whole-exome sequencing to identify genetic variants in patients with a positive response, but only in patients with idiopathic PAH.[7]

We report the long-term treatment of 12 years with CCB monotherapy in a patient

with SSc-PAH lacking known vascular smooth muscle gene variants.

CASE

A 48-year-old white woman with newly diagnosed PAH (World Health Organization functional class IIIa) and worsening dyspnea was referred to Mayo Clinic Florida Pulmonary Hypertension Clinic in 2006. She had a medical history of limited SSc with CREST syndrome with primary manifestations of esophageal reflux disease and Raynaud phenomenon that was diagnosed in 1993 with systemic symptoms and positive anti-nuclear and anti-centromere antibodies. Since 2004, she started to notice dyspnea on exertion while hiking inclines in altitude, which has gradually progressed to occur with minimal walking on flat surfaces and included presyncope. She underwent right heart catherization (RHC) before presentation that showed mean pulmonary arterial pressure (mPAP) of 44 mm Hg, pulmonary artery occlusion pressure (PAOP) of 9 mm Hg, and pulmonary vascular resistance (PVR) of 7.5 Wood units. Her only medications were aspirin, 81 mg, and esomeprazole, 40 mg, daily. Family history was negative for pulmonary hypertension and she never smoked cigarettes, used illicit drugs, or took anorexigens.

On initial presentation, body mass index (calculated as the weight in kilograms divided by the height in meters squared) was 21, with normal vital signs. Physical examination was positive for scattered telangiectasias, an accentuated P2, a 2/6 systolic murmur along the left sternal border, pitting edema (1^+) bilaterally in the pretibial region, sclerodactyly, and acrocyanosis. Pertinent negative findings include no jugular venous distension, clear lungs to auscultation and percussion, and no clubbing. Laboratory results, including a complete blood cell count with differential, coagulation panel, electrolytes, creatinine, brain natriuretic peptide, thyroid-stimulating hormone, and liver function tests, were all normal. Elevation of the antinuclear antibody titer using enzyme-linked immunosorbent assay at 10.5 units (normal, 0-1 units) and a positive anti-centromere antibody was confirmed.

A transthoracic echocardiogram (TTE) was performed that showed right ventricular systolic pressure of 51 mm Hg and a measured mPAP of 37 mm Hg based on right atrial pressure of 5 mm Hg and tricuspid regurgitant jet of 3.4 m/s.[8] The right ventricle had borderline hypertrophy with mild global hypokinesis. The left ventricle and atrium were of normal size and function with ejection fraction of 68% and no wall motion abnormalities.

The patient was able to walk 532 m while breathing room air on a 6-minute walk test. Radiography and computed tomography of the chest were performed, which showed no underlying lung disease. A ventilation/perfusion scan was negative for pulmonary embolism. Complete pulmonary function test results were normal, including a normal diffusion capacity. An RHC was repeated and revealed mPAP of 39 mm Hg, PAOP of 4 mm Hg, PVR of 7.5 Wood units, and cardiac index of 3.1 L/min/m^2.

A vasodilator trial was attempted during the RHC and the patient was responsive to 3 different vasodilators, including nifedipine, sildenafil, and epoprostenol. Specifically, 160 mg of oral nifedipine resulted in a decrease in mPAP to 28 mm Hg with no change in cardiac index (3.2 L/min/m^2), PAOP (5 mm Hg), or systemic blood pressure (mean arterial pressure, 83 mm Hg). The evaluation confirmed the diagnosis of SSc-associated PAH that was vasoresponsive to multiple acute vasodilators.

Immediately following the RHC, the patient was started on treatment with nifedipine extended-release tablets, 90 mg, twice daily. Six months later, she had improvement in her symptoms and was now World Health Organization functional class II. A repeat TTE demonstrated that the right ventricle had normalized in regard to size and function. Estimated mPAP remained at 37 mm Hg. She walked 646 m while breathing room air for a 6-minute walk test. After 10 years on this single regimen, her most recent RHC revealed mPAP of 27 mm Hg, PAOP of 8 mm Hg, PVR of 2.9 Wood units, and cardiac index of 4.2 L/min/m^2 (Table 1).

Because of the success of her treatment, the patient joined a research study looking to see if she had any gene variants that made her vasoresponsive. For this study, her blood was collected in a PAXgene (Qiagen) blood DNA tube. DNA was isolated and Sanger sequencing was performed. No variants were found in the following genes: *ADCY4*,

TABLE 1. Patient's Clinical Data at Baseline and Follow-up

	Initial	12-y Follow-up
World Health Organization functional class	IIIa	I
6-minute walk distance (m)	532	657
Right ventricular enlargement	Borderline	Normal
Right ventricular dysfunction	Mild	Normal
RHC mean pulmonary artery pressure (mm Hg)	39	27
RHC cardiac index (L/min/m^2)	3.1	4.2
RHC pulmonary vascular resistance (Wood units)	7.5	2.9

RHC = right heart catherization.

ADCY8, *GNAS*, *PLA2G4E*, *PPP1R12B*, *RAF1*, *ATP1A4*, *CACNA2D3*, *RYR2*, and *UQCR1* (Table 2; for expansion of gene symbols, use search tool at www.genenames.org).

The patient is currently 60 years old and still on monotherapy with nifedipine extended-release, 90 mg, twice daily for SSc-associated PAH. She has never been treated with immunosuppressants targeting the SSc; however, she has used symptomatic therapies, such as celecoxib and esomeprazole. Her most recent TTE revealed a right ventricle that was normal in size and function and a normalized mPAP.

DISCUSSION

In patients with PAH with a positive AVT result, multiple studies have shown improved survival if these patients are treated with a CCB.[2,5,9] Vasodilators used for AVT currently include inhaled nitric oxide, intravenous epoprostenol, or intravenous adenosine. The AVT is considered positive if mPAP decreases by at least 10 mm Hg and to a value less than 40 mm Hg, with increased or unchanged cardiac output and minimally affected systemic blood pressure.[10] Positive AVT results have been reported to be as high as 13.4% (17 of 127) in patients with drug-associated PAH to being absent in congenital heart disease–associated PAH.[4] In patients with connective tissue disease (CTD), such as SSc, the reported vasoreactivity response rate is 10.1% (17 of 168) of patients.[4] The risks associated with performing AVT, including hypotension and acute heart failure, when performed at pulmonary hypertension centers occur at a rate of less than 1% (76 of 7218).[11] The benefit is finding out whether a CCB could be used as a treatment option because they are among the least expensive PAH treatments because PAH-specific medications cost $2500 to $12,000 monthly.[12] In addition, CCBs are generally well tolerated.

Based on current guidelines, AVT should only be performed on patients with idiopathic PAH, heritable PAH, and PAH associated with drugs because of limited evidence (class IIIC recommendation) supporting the long-term effectiveness of CCB treatment only in these patients.[1,2,9] Of note, a positive AVT result does not guarantee clinical response from a CCB, as evidenced by an observational study showing that only 5% (38 of 557) of patients with idiopathic PAH with a positive AVT result treated with a CCB had improvement at 1 year.[2] There are no randomized clinical trials, but a few retrospective and observational studies exist evaluating CCBs in CTD-PAH. One retrospective study showed that the long-term

TABLE 2. Vasoreactive Pulmonary Arterial Hypertension Gene Variants Analyzed

Gene[a]	Position and Change	Observed Genotype
ADCY4	chr14:24787904:24787904:C:T	C
ADCY8	chr8:131826409:131826409:A:G	A
GNAS	chr20:57415640:57415640:C:T	C
PLA2G4E	chr15:42282330:42282330T:C	A
PPP1R12B	chr1:202407213:202407213:A:G	A
RAF1	chr3:12626428:12626428:T:C	T
ATP1A4	chr1:160129232:160129232:C:G	C
CACNA2D3	chr3:54913054:54913054:G:A	G
RYR2	chr1:237729972:237729972:C:T	C
UQCR10	chr22:30165696:30165696:T:A	Inconclusive

[a]For expansion of gene symbols, use search tool at www.genenames.org.

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effectiveness of CCB in PAH associated with CTD was only 0.6% (1 of 168) among all the patients tested with disease.[4]

Recently, there have been advances to mechanistically explain why some patients respond to CCB therapy while others do not. Whole-exome sequencing studies that compared patients who were vasoreactively responsive with those with nonresponsive idiopathic PAH demonstrated multiple genetic variants responsible for vascular smooth muscle contraction.[7] The genes identified were involved in cytoskeletal function and Wnt signaling pathway. Our patient was negative for these same gene variants, highlighting the need for further studies to help identify additional genetic susceptibility to specific treatments in all patients with PAH.

CONCLUSION

Because this case is the first to describe such a long-term successful treatment with CCB monotherapy in a patient with SSc-associated PAH and no vascular smooth variants, it exemplifies several exemptions to established guidelines and highlights multiple areas in PAH treatment that require further study. First, we recommend that AVT be considered in patients in all PAH subgroups unless clinically contraindicated, for example, cardiac index less than 2 L/min/m^2. First-line therapy in patients with positive AVT results should be a CCB because of reduced adverse effects and cost, but requires close follow-up because of a high failure rate. Additional mechanistic pathways other than the currently identified vascular smooth variants require further investigation, as highlighted by this patient.

Abbreviations and Acronyms: **AVT** = acute vasoreactivity testing; **CCB** = calcium channel blocker; **CREST** = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; **CTD** = connective tissue disease; **mPAP** = mean pulmonary arterial pressure; **PAH** = pulmonary arterial hypertension; **PAOP** = pulmonary arterial occlusion pressure; **PVR** = pulmonary vascular resistance; **RHC** = right heart catherization; **SSc** = systemic sclerosis; **TTE** = transthoracic echocardiogram

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