

Letter to the Editor

Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension has a poor prognosis quoad vitam et valitudinem. Herein, we report on a middle-aged woman affected by idiopathic pulmonary arterial hypertension whose quality of life and exercise tolerance improved remarkably after a six-month course of treatment with the long-acting phosphodiesterase-5 inhibitor tadalafil.

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1. Introduction

Impaired modulation of pulmonary vascular tone due to changes at an endothelial cell level leading to defective production of endogenous vasodilators such as nitric oxide and prostacyclin critically contributes to the development and the progressive nature of pulmonary arterial hypertension (PAH), providing the rationale for the clinical use of different compounds aimed to correct such an abnormal vascular function [1].

Among others, sildenafil, a selective inhibitors of the phosphodiesterase-5 isoform, which is specific for the breakdown of cyclic guanosine 3,5'-monophosphate (cGMP), the second messenger through which nitric oxide modulates pulmonary vascular tone, has gained increasing attention as a safe and effective therapy of adult and children with PAH [2,3]. Accordingly, sildenafil has recently been recommended by the European Society of Cardiology for the treatment of those patients who have failed to respond to or are not candidates for other therapies (Grade=I; Level of

evidence=A) [4]. However, because of its short half-life (~4 h) [5], sildenafil requires many daily administrations, which in the long term may affect treatment adherence and may be costly.

We recently reported the case of an elderly woman with end-stage idiopathic PAH whose pulmonary hemodynamics, arterial oxygenation, clinical and functional status were greatly improved after six month-course of treatment with tadalafil (20 mg orally every other day) [6], a phosphodiesterase-5 inhibitor with an half-life nearly 5-fold greater than sildenafil [7]. Herein, we describe the clinical efficacy of the same tadalafil regimen in a middle-aged woman with idiopathic PAH of moderate severity.

2. Case report

A 42-year-old woman with a diagnosis of idiopathic PAH attended our hospital because of fatigue and effort dyspnea (New York Heart Association/World Health Organization class III). She was taking diuretics (furosemide 25 mg+spironolactone 50 mg qd), and oral anticoagulant (warfarin) tailored to an International Normalized Ratio target of 2.0–3.0, and she was receiving low-flow supple-

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mental oxygen to maintain peripheral oxygen saturation above 90% during daily activities. Initially, the patient was prescribed slow-release nifedipine, which was subsequently withdrawn because of symptomatic arterial hypotension with a relatively low dose (30 mg bid).

At basal examination, the patient had no sign of hydropic decompensation; blood pressure was 108/72 mm Hg, pulse was 89 beats/min and regular, respiratory rate was 22 breath/min and arterial PO_2 , while breathing ambient air, was 68 mm Hg. She had a total score of 35 at the Minnesota Living With Heart Failure Quality of Life Questionnaire. Doppler-echocardiography showed moderate dilation and hypertrophy of the right ventricle (longitudinal diameter=50 mm; transversal diameter=40 mm; free-wall thickness=12 mm), and severe pulmonary arterial hypertension (estimated peak pulmonary arterial pressure of 100 mm Hg). During a treadmill exercise test with the Cornell's, the patient achieved a ventilatory peak oxygen uptake of 13 ml/kg/min. The test was interrupted after 6 min because of dyspnea and fatigue. Thus, with the patient's informed consent, we prescribed tadalafil (20 mg orally every second day) in addition to background therapy.

After six months of tadalafil treatment, the patient did not report any untoward effect nor she did complain of hydropic decompensation. Diuretics were progressively reduced until they were withdrawn. The patient's blood pressure was 122/66 mm Hg, her pulse was 72 beats/min, her respiratory frequency was 18 breath/min and her arterial PO_2 , while breathing ambient air, was 92 mmHg. The total score at the Minnesota Living With Heart Failure Quality of Life Questionnaire was 7. Doppler-echocardiography documented a substantial attenuation of right ventricular dilation and hypertrophy (longitudinal diameter=39 mm; transversal diameter=31 mm; free-wall thickness=8 mm), associated with a remarkable reduction of estimated peak pulmonary arterial pressure (76 mm Hg). Consistent with the patient's perception of a better functional status (New York Heart Association/World Health Organization class II), cardiopulmonary exercise testing documented an objective improvement of effort tolerance (exercise time=8 min; ventilatory peak oxygen uptake=15 ml/kg/min).

3. Discussion

In line with our former report of an elderly patient affected by end-stage idiopathic PAH [6], we found that, in a middle-aged woman with idiopathic PAH of moderate severity, a six month-course of treatment with tadalafil (20 mg every second day) is safe and resulted in greatly improved pulmonary hemodynamics and arterial oxygenation. These findings were paralleled by reverse remodeling of the right ventricle, a striking improvement in quality of life, and a slight increase in exercise capacity (Fig. 1). Indeed, improvement in exercise tolerance, as assessed by

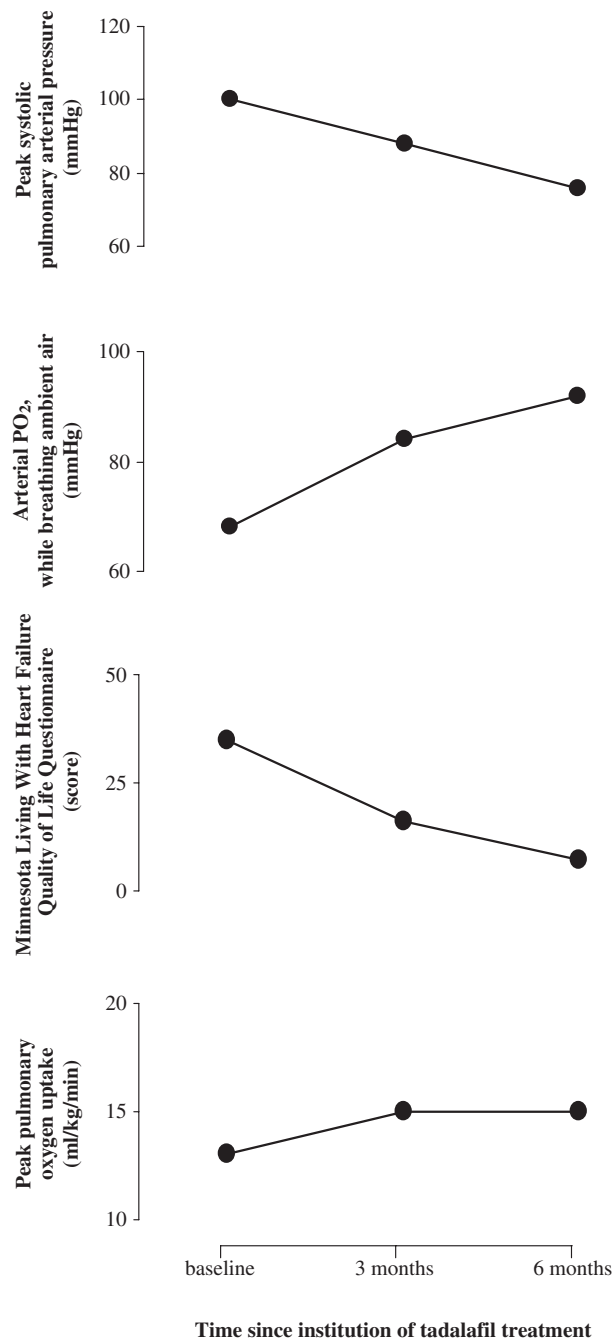


Fig. 1. Trends in pulmonary hemodynamics, arterial oxygenation, quality of life and exercise capacity consequent to tadalafil therapy.

means of cardiopulmonary exercise testing, was less marked than that expected from the patient's perceived functional status. Although surprising, this finding is consistent with results of trials of patients with PAH treated with prostacyclin analogues and endothelin-1 receptor antagonists in which cardiopulmonary exercise testing failed to confirm improvements observed with the six-minutes walking test [8,9], thereby suggesting a lack of sensitivity of cardiopulmonary exercise testing in measuring response to treatment that has less effect on maximal than on submaximal exercise.

Our experience in the treatment of patients with idiopathic PAH provides the rationale for a double-blind, randomized and adequately powered trial to evaluate optimal tadalafil dosing and compare the clinical efficacy and costs of tadalafil versus sildenafil in the treatment of idiopathic PAH.

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References

- [1] Gibbs JS, Broberg CS, Gatzoulis MA. Idiopathic pulmonary arterial hypertension: current state of play and new treatment modalities. *Int J Cardiol* 2004;97(Suppl 1):7–10.
- [2] Karatza AA, Bush A, Magee AG. Safety and efficacy of Sildenafil therapy in children with pulmonary hypertension. *Int J Cardiol* 2005; 100:267–73.
- [3] Chockalingam A, Gnanavelu G, Venkatesan S, et al. Efficacy and optimal dose of sildenafil in primary pulmonary hypertension. *Int J Cardiol* 2005;99:91–5.
- [4] Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the european society of cardiology. *Eur Heart J* 2004;25:2243–78.
- [5] Cheitlin MD, Hutter Jr, AM, Brindis RG, et al. ACC/AHA expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. American college of cardiology/American heart association. *J Am Coll Cardiol* 1999;33:273–82.
- [6] Palmieri EA, Affuso F, Fazio S, Lembo S. Tadalafil in primary pulmonary arterial hypertension. *Ann Intern Med* 2004;141:743–4.
- [7] Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002;168:1332–6.
- [8] Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:2115–25.
- [9] Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; 169:441–7.