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Sildenafil for Pulmonary Hypertension Complicating Dermatomyositis

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S u m m a r y. Dermatomyositis is a rare autoimmune disease with a high morbidity rate. Diagnosis requires the demonstration of tissue inflammation involving mainly the muscles as well as the typical rash (heliotrope rash or Gottron papules) (1,2). It is not infrequently the first sign of an associated malignancy or may be part of another connective tissue disease. Treatment traditionally involves steroids, intravenous immunoglobulin or immunosuppressants (1,2). Extramuscular systems affected beside the skin include the heart (arrythmias, congestive heart failure, and myocarditis), lung (fibrosing alveolitis, aspiration and most notably interstitial lung disease), gastrointestinal tract, and joints. Pulmonary arterial hypertension is a rare but lethal complication which usually develops secondary to lung involvement. Here we report a patient with severe pulmonary hypertension secondary to dermatomyositis who improved dramatically when treated with oral sildenafil.

CASE REPORT

The patient, a 55-yr-old woman with an 8-yr history of dermatomyositis under steroids, intravenous immunoglobulin and immunosuppressants without any evidence of an associated malignancy, was diagnosed with severe pulmonary hypertension (PH) in February 2004 (WHO class III) during a work-up for persisting minimal effort tolerance, despite clinical and laboratory evidence of improvement of her primary disease. Plain chest radiography repeatedly exhibited a bibasilar linear attenuation pattern but high resolution CT scanning of her chest was not indicative of fibrosis or thickening of the interlobular septa. The echocardiogram showed normal sized left ventricle (slightly enlarged left atrium) with good systolic function (EF 62-64%), dilated right heart chambers, severe tricuspid regurgitation and a systolic pulmonary pressure of 90-95 mmHg. At the time neither a right heart catheterization nor a 6-min walk test were feasible because the patient developed severe shortness of breath after a max. continuous walking distance of approximately 20 m; also the patient was reluctant to undergo any invasive procedure. The patient's history included surgery for interatrial communication (patent foramen ovale) in 1991 without any evidence of PH pre- and post-operatively.

Treatment for PH/ cardiac failure was initiated including diuretics, oral anticoagulation (warfarin) and Ca channel blockers (3-5). Due to the severity of the findings, bosentan, a non-selective endothelin receptor antagonist, recently approved for primary pulmonary hypertension, was added, at an initial dose of 62.5 mg twice daily, which was escalated to125 mg twice daily after four weeks. The dose was weaned back to 62.5 mg twice daily and the drug was completely discontinued three months later because the patient developed severe peripheral oedema, which only partially responded to diuretics, without any alleviation of her PH symptoms.

In January 2005 the patient was started on oral sildenafil at a dose of 0.5 mg/kg (25 mg) twice daily. One month later, despite no alteration of her echocardiographic findings, the patient reported improving ability to move around within her residence, and being increasingly able to perform her domestic activities. After six months of treatment the patient accepted heart catheterization which showed a systolic pulmonary pressure of 75mmHg with a pulmonary capillary wedge pressure of 19 mmHg, and her completed 6-min walk test has improved to 200m in total. The patient has not developed any clinical or laboratory side effects so far.

DISCUSSION

Sildenafil, a potent vasodilator, which increases the activity of endogenous nitric oxide via inhibition of the breakdown of cGMP by phosphodiesterase type 5, has not been officially approved for the treatment of primary pulmonary hypertension yet. Experience with sildenafil in PH is therefore limited. Emerging data is supportive of a synergistic role of this pharmaceutical agent in combination therapy

with prostacyclin analogues or endothelin receptor antagonists in cases of refractory primary PH (4,6-8). In our case however, and in agreement with a short-term, small scale study published recently (9), sildenafil per se was able to significantly improve both pulmonary haemodynamics and functional capacity of the patient, as expressed by the 6-min walk test. Efficacy was sustained long-term and no adverse events were observed in association with the treatment. Of particular interest is the fact that the patient reported improvement of her functional state before any alterations of her pulmonary haemodynamics became evident. The potential utility of sildenafil has particular appeal as a long-term treatment due to its ease of administration. Caution needs to be taken however in the treatment of patients with severe lung disease, due to the impairment and potential deterioration of the ventilation/ perfusion matching in animal models (5). Large-scale studies will be needed in order to compare its efficacy, side effects and safety with other therapies, as well as to determine its role in combination therapy.

REFERENCES

1. Christopher-Stine L., Plotz P.H.: Adult inflammatory myopathies. *Best. Pract. Res. Clin. Rheumatol. 18*: 331-344 (2004)

2. Chinoy H., Ollier W.E., Cooper R.G.: Have recent immunogenetic investigations increased our understanding of disease mechanisms in the idiopathic inflammatory myopathies? *Curr. Opin. Rheumatol. 16*: 707-713 (2004)

3. Humbert M., Sitbon O., Simonneau G.: Treatment of pulmonary arterial hypertension. *N. Engl. J. Med. 351*: 1425-1436 (2004)

4. Gibbs J.S., Broberg C.S., Gatzoulis M.A.: Idiopathic pulmonary arterial hypertension: current state of play and new treatment modalities. *Int. J. Cardiol. 97 (Suppl 1)*: 7-10 (2004)

5. Badesch D.B., Abman S.H., Ahearn G.S., Barst R.J., McRory D.C., Simonneau G., et al.: American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension. ACCP Evidence-Based Clinical Practice Guidelines. *Chest 126 (1 Suppl)*: 35S-62S (2004)

6. Wilkins M.R., Paul G.A., Strange J.W., Tunariu N., Gin-Sing W., Banya W., et al.: Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. Am. J. Respir. Crit. Care Med.: epub March 4, 2005

7. Hoeper M.M., Faulenbach C., Golpon H., Winkler J., Welte T., Niedermeyer J.: Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur. Respir. J. 24*: 1007-1010 (2004)

8. Kataoka M., Satoh T., Manabe T., Anzai T., Yoshikawa T., Mitamura H., et al.: Oral sildenafil improves primary pulmonary hypertension refractory to epoprostenol. *Circ. J. 69*: 461-465 (2005)

9. Chockalingam A., Gnanavelu G., Venkatesan S., Elangovan S., Jagannathan V., Subramaniam T., et al.: Efficacy and optimal dose of sildenafil in primary pulmonary hypertension. *Int. J. Cardiol. 99*: 91-95 (2005)