

Intermittent Epoprostenol Infusions in Systemic Lupus Erythematosus Associated Pulmonary Hypertension—A Series of Three Cases

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Abstract

Introduction: Pulmonary hypertension (PHT) associated with systemic lupus erythematosus (SLE) has a grave prognosis. Continuous prostacyclin infusion significantly reduces pulmonary arterial pressure (PAP) and may improve survival in patients with primary and secondary PHT. We report our experience with intermittent epoprostenol (EPO) infusion in SLE patients with PHT. **Clinical Characteristics:** We reviewed patients with SLE associated PHT who were treated with intermittent EPO infusions in 1998. All 3 patients had severe PHT, with maximum systolic PAP (PASP) of 58, 96 and 67 mm Hg, respectively, when measured using Doppler echocardiography, and were in New York Heart Association functional class III. **Treatment:** All patients were given 6 infusions of EPO monthly via peripheral venous access without significant side effects. **Outcome:** The PASP of all patients remained stable during the therapy. The therapeutic response as measured by patient symptoms and PASP was variable. No patient had significant reduction of PASP during the 6-month treatment period. Two patients developed rebound elevation of PASP after cessation of treatment, while the PASP of the other patient remained stable for 10 months. **Conclusion:** Although intermittent EPO infusion did not substantially reduce PASP, it prevented further rise in PAP during the treatment period, suggesting that this regimen may benefit a subset of SLE patients with PHT.

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Key words: Connective tissue diseases, Epoprostenol, Pulmonary hypertension, Systemic lupus erythematosus

Introduction

Pulmonary hypertension (PHT) is seen in 0.5% to 14% of systemic lupus erythematosus (SLE) patients¹⁻³ and is associated with a grave prognosis. The overall 2-year mortality is more than 50% despite vasodilators, anticoagulants, systemic corticosteroids and cytotoxic drugs.⁴

The pathogenesis of PHT in SLE is not well understood and multiple aetiological factors are probably involved. Vasculitis, pulmonary fibrosis, valvular heart disease and pulmonary thromboembolism are all possible causes. SLE patients with PHT have a higher frequency of Raynaud's phenomenon,¹ suggesting that pulmonary arterial vasospasm may also contribute to PHT. Histologically, the pulmonary vascular abnormalities of patients with SLE associated PHT are similar to those of patients with primary PHT.³ An increase in the release of thromboxane A₂ and a decrease in the release of prostacyclin in patients with PHT

suggests a possible role for endothelial dysfunction and abnormal vascular response.⁵

Prostacyclin produced by the vascular endothelium is a potent short acting vasodilator and inhibitor of platelet aggregation. Continuous intravenous prostacyclin infusion improves exercise tolerance, haemodynamic variables, quality of life and survival in patients with primary pulmonary hypertension.^{6,7} This treatment has also been shown to improve exercise capacity and cardiopulmonary haemodynamics in patients with PHT, with or without lung pathology, due to scleroderma/CREST syndrome and other connective tissue diseases.^{8,9} Case reports and case series suggest the efficacy of continuous intravenous prostacyclin infusion in PHT due to SLE.^{10,11} However, continuous infusions carry the risk of line-related complications, such as serious infection, catheter thrombosis and pump failure, which are potentially life threatening.⁸⁻¹¹ The development of tolerance in some patients necessitates continuous dose

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escalation and may contribute to the high cost of the treatment.

Some of these drawbacks may be minimised by using an intermittent infusion regime via a peripheral intravenous line. However, the efficacy of intermittent infusion is not known. Intermittent iloprost infusion has been reported to be beneficial in PHT in scleroderma.¹² There has been only one report of intermittent epoprostenol (EPO) usage in a case of SLE, which suggested that intermittent, monthly low-dose iloprost infusion reduced pulmonary artery pressure (PAP).¹³ We herein describe our experience with intermittent EPO infusion in 3 patients with SLE associated PHT.

Case Series

We reviewed our series of patients with SLE and PHT treated with monthly EPO infusions in 1998. Medical records, imaging studies and laboratory investigations were reviewed using a standardised, data abstraction form. There were 3 patients. All were female and had a diagnosis of pulmonary hypertension made in 1998 when they presented with increasing dyspnoea, reduced effort tolerance, and a New York Heart Association (NYHA) class III functional status. All of them were non-smokers. Physical examination showed right ventricular heave and accentuated pulmonic component of the second heart sound. Table I shows their clinical characteristics. All patients fulfilled the following criteria:

- 1) diagnosis of SLE based on American College of Rheumatology criteria;¹⁴
- 2) confirmation of PHT by Doppler echocardiography. PHT was defined as systolic PAP (PASP) more than 30 mm Hg; and

- 3) exclusion of other causes of pulmonary hypertension, such as a past history of appetite suppressant usage, congenital or valvular heart disease (based on findings on 2D echocardiography), and diffuse pulmonary fibrosis [based on findings of high resolution computed tomographic (CT) scan of the thorax].

Although 2 of the patients had a history of pulmonary embolism prior to the diagnosis of PHT, this was not thought to be the aetiology of the PHT for the following reasons:

- 1) PASP became elevated a few years after the diagnosis of pulmonary embolism despite the patients being adequately anti-coagulated,
- 2) PASP continued to rise in both these patients during the follow up period despite anti-coagulation,
- 3) recurrent pulmonary embolism was excluded by repeated ventilation-perfusion scan or spiral CT thorax scanning.

All patients were given intravenous infusions of EPO via a peripheral line every month for 6 months. EPO infusion was started at the rate of 2.5 ng/kg/min and increased by 1.25 ng/kg/min every 30 minutes to a maximum of 7.5 ng/kg/min or the maximum infusion rate that the patient could tolerate. The infusion was given at the maximum tolerated rate; 15 hours daily for 3 days. If any adverse events such as hypotension, flushing, headache, nausea, vomiting and/or abdominal colic occurred, the infusion rate was reduced to the maximum tolerated dose. Blood pressure was monitored every 30 minutes from the commencement of the infusion until 1 hour after completion. Anti-hypertensive agents were withheld on the days of the infusion.

Changes in PASP were measured by 2-dimensional

TABLE I: PATIENTS' CLINICAL CHARACTERISTICS AND TREATMENT AT BASELINE

Patient	Race	Age (y)	SLE manifestations	Disease duration prior to diagnosis of PHT (y)	Investigations	Treatment
1	Chinese	24	Arthritis, malar rash, alopecia, oral ulcers, class IVb nephritis	3	ANA+ Anti-dsDNA+ ACA+ LAC-	Warfarin, Aspirin, Nifedipine, Prednisolone, Plaquenil, Captopril, IV cyclophosphamide monthly for 1 year (1997)
2	Chinese	35	Arthralgia, pleuritis, malar rash, oral ulcers, class V nephritis, stroke, renal vein thrombosis, deep vein thrombosis, history of pulmonary embolism (1x)	16	ANA+ Anti-dsDNA+ ACA+ LAC-	Warfarin, Aspirin, Adalat R, Captopril, Prazosin, Methyldopa, Prednisolone, Azathioprine
3	Malay	29	Arthralgia, alopecia, oral ulcers, history of pulmonary embolism (1x)	1	ANA+ Anti-dsDNA+ ACA- LAC+	Warfarin, Plaquenil, Diltiazem, Lasix, Span K

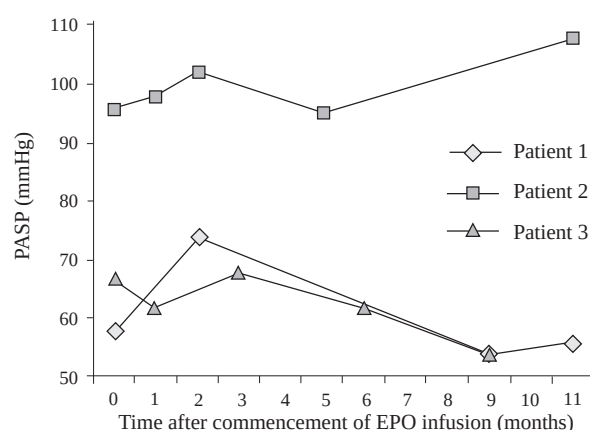


Fig. 1. Changes in systolic pulmonary artery pressure in 3 SLE patients treated with monthly epoprostenol infusion.

Doppler echocardiography as all the patients refused invasive diagnostic procedure, i.e. pulmonary artery catheterisation. A change in PASP of more than 5 mm Hg was regarded as significant.

The clinical course of these 3 patients after EPO infusion was studied. Figure 1 shows changes in PASP from the commencement of monthly intermittent EPO infusions to 5 months after completion. Our patients tolerated the EPO infusion well except for mild headache and flushing. All 3 patients had severe PHT, with a maximum PASP of 58, 96 and 67 mm Hg, respectively, at initiation of the therapy. At the end of 6 months, 2 patients (patients 1 and 3) had symptomatic improvement and improved effort tolerance, with concomitant improvement in their functional status from NYHA class III to NYHA class II. Patient 2 did not improve symptomatically. Her functional status remained as NYHA class III.

More than a year after completion of the EPO treatment (not shown in Fig. 1), the PASP for patient 1 remained stable at 56 mm Hg (16 months after completion) with functional status also remaining stable at NYHA class II. The PASP for patient 2 had risen to 116 mm Hg (14 months after completion), although her functional status remained stable at NYHA class III. The PASP for patient 3 had escalated to 79 mm Hg (13 months after completion), with the functional status deteriorating back to NYHA class III.

Among the 3 patients, only patient 2 did not receive monthly IV cyclophosphamide. Patient 1 had IV cyclophosphamide for 6 months prior to the commencement of the EPO infusion therapy for her active nephritis. In spite of this cytotoxic therapy, her PASP remained high. Whereas patient 3 had IV cyclophosphamide for a year only, after completion of the EPO infusion therapy in an attempt to reduce the PASP further.

Discussion

Treatment of SLE associated PHT has been difficult and unsatisfactory. Various treatment modalities including vasodilators, anticoagulation, oxygen therapy, corticosteroids and immunosuppressive agents have been used with variable results.³ The use of intermittent EPO in the treatment of PHT in SLE was previously reported to be useful in 1 SLE patient.¹³ The results of our study of 3 more cases further suggest that intermittent EPO infusion may be of benefit in the treatment of some SLE patients with PHT. Possible mechanisms of action of EPO in PHT include improvement in vasospasm⁶ and remodelling of pulmonary vasculature.¹⁵ Continuous EPO infusions had been shown to have some beneficial effects in PHT secondary to connective tissue diseases.⁸⁻¹¹ The connective tissue diseases studied include SLE, scleroderma, mixed connective tissue disease and primary Sjogren's syndrome. Although all the patients studied improved symptomatically and haemodynamically, they are exposed to the risk of drug delivery system-related adverse events, in addition to the side effects of EPO.^{6,9} With intermittent monthly EPO infusions, the drug delivery system-related adverse events may be minimised, as illustrated by our series, where none of the 3 patients developed such an event.

Immunosuppressants have been used to treat PHT in SLE as vasculitis has been implicated as a contributing factor. This is based on the results of the pathologic examination of lung tissue in SLE patients with PHT demonstrating deposition of immune complex and complements.³ A few case reports and case series^{16,17} have reported benefit in SLE patients with PHT treated with oral or monthly intravenous cyclophosphamide. Most of the patients in these reports did not have active SLE. In our study, the 2 patients (patients 1 and 3) who had monthly intravenous cyclophosphamide did do better in terms of the duration of time for which the PASP was controlled.

The optimal regime for EPO infusion and the appropriate duration of such treatment is not known. Our infusion regime was based on studies of the use of intermittent prostacyclin infusions in Raynaud's syndrome¹⁸ and scleroderma associated PHT.¹² We increased the duration of infusion on the premise that it may improve the clinical response with extension of the duration of its effect until the next monthly infusion. Although our data showed that intermittent EPO infusions may have a beneficial effect in SLE patients in that the PASP remained stable during the 6 months of therapy, the effects of EPO appear to have gradually diminished with time in 2 of 3 patients when the treatment was discontinued. As shown in Figure 1, patients 2 and 3 showed an increase in PASP above their baseline values, 10 and 6 months after cessation of EPO respectively. However, the PASP of patient 1 was lowered, with Doppler

echocardiography 16 months after cessation of EPO infusions showing a PASP of 56 mm Hg (compared to 62 mm Hg at the end of intermittent monthly EPO infusion). Our data suggest that extension of EPO infusion beyond a 6-month period may be beneficial, perhaps at an increased interval between infusions.

Acute rebound PHT is a potentially life-threatening complication in patients receiving chronic EPO infusion with short-term interruptions of drug delivery.¹⁹ However, none of our patients developed acute cor pulmonale or hypoxaemia after monthly EPO infusion that might suggest that a rebound worsening of PASP had occurred. In the recently published trials on aerosolised prostacyclin, no clinical or haemodynamic signs of rebound PHT was noted, except for fluctuations in exercise capacity between inhalation.²⁰

Life-threatening thrombocytopaenia has also been described in SLE patients with PHT and otherwise quiescent disease who were given EPO infusion.²¹ Its exact aetiology remains unknown, although it has been suggested that platelet destruction may occur in the pulmonary vascular bed. None of the 3 patients reported here developed thrombocytopaenia.

Conclusion

Our experience in a small number of patients suggests that intermittent EPO can be given safely in SLE associated PHT. It may have a role in retarding further rises of PASP in SLE patients with PHT, although it did not appear to reduce PASP. This effect appears to diminish after intermittent EPO is ceased. A larger clinical trial could be designed to confirm these observations. With recent reports of successful use of inhaled prostacyclin²⁰ in primary pulmonary hypertension, there will be more therapeutic options for the treatment of PHT in patients with SLE.

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