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SHORT COMMUNICATION

Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia

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Background and objective: Acute exacerbations of interstitial pneumonias (IP) can occasionally occur, and have an extremely poor prognosis. Recently, direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) was shown to have a beneficial effect in acute exacerbations of IPF. However, little is known about the efficacy of PMX-DHP in acute exacerbations of other IP. This study investigated the effectiveness and safety of PMX-DHP in acute exacerbations of IP.

Methods: The study subjects consisted of five patients with an acute exacerbation of IP, including three with IPF, one with idiopathic interstitial pneumonia (IIP) with atypical radiological findings of IPF, and one with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related IP. The patients were treated with two courses of 3–12 h each of PMX-DHP, concurrently with corticosteroids alone or plus cyclophosphamide.

Results: After two courses of PMX-DHP, the PaO_2/fraction of inspired oxygen (FiO_2) (P/F) ratio increased rapidly from an average of 93 to 260 mm Hg, and there was radiological improvement in all patients. However, one patient treated for 3 h each time eventually died of respiratory failure, and two patients treated for 6 h each time died from respiratory infections. The other two patients were treated for 12 h each time, and the therapeutic effects lasted longer, with both surviving longer than 48 days. No adverse effects were detected apart from thrombocytopaenia.

Conclusion: PMX-DHP therapy was safe and effective in improving oxygenation in acute exacerbations of IPs, either with corticosteroids alone or plus cyclophosphamide, and may be beneficial for the treatment of this condition.

Key words: acute-phase reaction, haemoperfusion, interstitial pneumonia, oxygenation, polymyxins.

INTRODUCTION

Patients with interstitial pneumonia occasionally show rapid deterioration during the course of their illness. This phenomenon, which is called acute exacerbation of interstitial pneumonia, was first described by Kondoh *et al.* in IPF.[1] Pathological findings in acute exacerbations are reported as diffuse alveolar damage (DAD) superimposed on chronic interstitial fibrosis.[2] Recently, acute exacerbation of IPF (AE-IPF) has been

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widely recognized as a distinct clinical condition, without identifiable causes for the deterioration of IPF,[3–7] and has been shown to occur in approximately 9.6–12.0% of IPF patients at some time during their clinical course.[4,6,7] More recently, acute exacerbation has been also reported in other interstitial pneumonias, such as idiopathic non-specific interstitial pneumonia (NSIP),[8] interstitial pneumonia associated with collagen vascular disease (CVD-IP),[9–11] and with microscopic polyarteritis.[12] This condition has been shown to be generally resistant to intensive anti-inflammatory and immunosuppressive therapy, such as high doses of corticosteroids plus immunosuppressive agents.[5–7] The prognosis of patients with acute exacerbations has been reported to be extremely poor, with a high mortality rate (80–85%) in AE-IPF.[5–7] A new therapy with high efficacy is therefore needed for the treatment of acute exacerbations.

Direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) has been used for the treatment of sepsis, to remove plasma endotoxin which is produced by Gram-negative bacteria, and has proven to be highly effective in this fatal condition.[13–15] However, several studies have also reported that PMX-DHP therapy was beneficial in patients with Gram-positive bacterial infection,[14,15] or with endotoxin-negative infection.[16] Interestingly, treatment with PMX-DHP was shown to improve pulmonary oxygenation in patients with ARDS, which is pathologically characterized by DAD.[16–18] This prompted physicians to consider PMX-DHP as a potential therapy for acute exacerbation of interstitial pneumonia, which also shows a histological pattern of superimposed DAD. The most recent study by Seo *et al.* clearly demonstrated that PMX-DHP had a beneficial effect in AE-IPF.[19] However, little is known about the efficacy of PMX-DHP in acute exacerbations of other interstitial pneumonias, such as NSIP or CVD-IP. This study investigated the effectiveness and safety of PMX-DHP therapy in patients with acute exacerbations of a variety of interstitial pneumonias, including IPF, idiopathic interstitial pneumonia (IIP) with atypical radiological findings of IPF, and CVD-IP. Changes in the serum levels of parameters associated with lung injury, such as cytokines and high-mobility group box protein 1 (HMGB1), were also measured during PMX-DHP therapy.

METHODS

Study design and subjects

This was a prospective study of five consecutive patients with acute exacerbations of interstitial pneumonia; of the five patients, three had IPF, one had IIP with atypical radiological findings of IPF, and one had myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related interstitial pneumonia. Of the three IPF patients, one was diagnosed by surgical lung biopsy, and two were diagnosed clinically, based on the American Thoracic Society/European Respiratory Society international consensus statement on IIP.[20] In the three IPF patients, acute exacerbations occurred at 36, 40 and 45 months after the initial diagnosis of IPF. The IIP patient with atypical radiologic findings of IPF showed thickening of bronchovascular bundles, no honeycombing, and no subpleural predominance. There was no underlying disease causing the interstitial pneumonia. This patient developed an acute exacerbation 7 months after the initial diagnosis of IIP. The patient with MPO-ANCA-related interstitial pneumonia had a surgical lung biopsy 10 years prior to the acute exacerbation, and had a histological diagnosis of fibrotic NSIP. The biopsy specimens did not show vasculitis or capillaritis. This patient was lost to follow up after the biopsy, and his chronic interstitial pneumonia deteriorated without medication. He developed an acute exacerbation 10 years after the surgical lung biopsy. The serum level of MPO-ANCA was elevated (55 U/mL) at the time of biopsy, and rose further to 254 U/mL at the time of the acute exacerbation. Diffuse alveolar haemorrhage was excluded by BAL in this patient.

The patients were all male, with ages ranging from 68 to 82 years (mean 73 years). The diagnosis of acute exacerbation was based on the criteria of Kondoh *et al.*[1] and Akira *et al.*[3] with slight modifications: (i) aggravation of dyspnoea within 1 month; (ii) newly developing pulmonary ground glass opacity (GGO) and consolidation on high-resolution CT (HRCT) of the chest; (iii) deterioration of hypoxaemia ($PaO_2 \geq 10$ mm Hg compared with a previously stable state); and (iv) absence of apparent infection, pneumothorax, pulmonary thromboembolism or heart failure. To exclude infection, serum antibody titres of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae,* as well as plasma endotoxin levels, were measured at two different times. Blood and sputum cultures were performed, as was PCR to detect *Pneumocystis jiroveci* in the sputum, and a *Cytomegalovirus* antigenaemia assay. BAL was performed on the two intubated patients, one with IPF and one with MPO-ANCA-related interstitial pneumonia.

The primary end-point in this study was the survival rate 30 days after the initiation of PMX-DHP treatment, and the secondary end-point was improvement of the acute exacerbation of interstitial pneumonia. Improvement of the acute exacerbation of interstitial pneumonia was defined as two or more of the following: (i) improvement of clinical symptoms; (ii) improvement of abnormal opacities on CXR and/or HRCT; and (iii) increase in the PaO_2/fraction of inspired oxygen (FiO_2) (P/F) ratio by more than 30% from baseline. The study protocol was approved by the Ethics Committee of the Hamamatsu University School of Medicine, and written informed consent was obtained directly from each patient.

Treatment for acute exacerbation

Immediately after diagnosis of an acute exacerbation, patients were treated with high dose corticosteroid pulse therapy (methylprednisolone, 1000 mg/day) for 3 days followed by a tapering dose of prednisolone.

When the effect of initial treatment was inadequate, cyclophosphamide pulse therapy (500 mg/2 weeks) was added. In patients requiring mechanical ventilation, intravenous sivelestat sodium hydrate was administered.

PMX-DHP therapy

Concomitant with the administration of corticosteroid alone or with cyclophosphamide, PMX-DHP therapy (PMX; Toray Medical, Tokyo, Japan) was administered. A double-lumen catheter was inserted into a femoral vein. PMX-DHP was administered for 3–12 h at a flow rate of 80–100 mL/min, and subsequently repeated once within 24 h. Nafamostat mesilate and/or heparin sodium were used as anticoagulants.

Measurement of cytokines and high mobility group box protein 1

Blood samples were taken before and after PMX-DHP therapy. The serum levels of IL-6, IL-8, IL-10 and HMGB1 were measured using ELISA. The plasma concentration of neutrophil elastase was determined in four patients (patients 1–4) using enzyme immunoassay.

RESULTS

Clinical effects of PMX-DHP

Of the five patients treated with PMX-DHP, one patient with IPF (Case 3) had received corticosteroid and cyclosporine for 3 years, while the other four were not on any regular medication. A summary of the clinical characteristics, laboratory results and physiological findings on admission is shown in Table 1. Although WCC and CRP levels were increased prior to treatment, blood cultures and plasma endotoxin were negative in all cases. Serum levels of LDH, KL-6 and surfactant protein D (SP-D), all markers of interstitial pneumonia, were elevated, and the P/F ratio was less than 200 mm Hg on admission in all cases. A summary of the treatments for acute exacerbations, including PMX-DHP, is shown in Table 2. In patients 1–3, PMX-DHP was started after 3 days of methylprednisolone pulse therapy. In patients 4 and 5, PMX-DHP was administered concomitantly with the initial methylprednisolone pulse therapy. The duration of PMX-DHP varied from patient to patient. Patient 1, patients 2 and 3, and patients 4 and 5 received 3 h, 6 h and 12 h of PMX-DHP therapy, respectively, twice within a 24-h period.

The clinical courses of the patients treated with PMX-DHP are shown in Fig. 1. In patients 1–3, the P/F ratios declined rapidly to less than 100 mm Hg with deterioration of CXR findings (Fig. 1a) despite the initial methylprednisolone pulse therapy, and the serum LDH levels increased or remained high

Table 1 Clinical characteristics, laboratory results and physiological findings on admission

Patient No.	Age (years)	Gender	Underlying disease	Previous therapy for interstitial pneumonia	Laboratory results							
					WCC ($\times 10^9$/L)	CRP (mg/L)	LDH (IU/L)	KL-6 (U/mL)	SP-D (ng/mL)	Endotoxin (pg/mL)	Blood culture	P/F ratio (PaO_2/FiO_2; mm Hg)
1	72	M	IIP	—	9.4	148	340	904	169	<0.8	Negative	188
2	71	M	MPO-ANCA-related IP	—	15.3	106	253	2300	104	<0.8	Negative	134
3	82	M	Histologically proven IPF	PSL 10 mg/day + cyclosporin A 100 mg/day p.o.	7.1	38	328	1300	157	<0.8	Negative	175
4	68	M	Clinical IPF	—	11.4	100	231	481	260	<0.8	Negative	186
5	71	M	Clinical IPF	—	8.4	35	344	2550	552	<0.8	Negative	195

IIP, idiopathic interstitial pneumonia; IP, interstitial pneumonia; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; p.o., *per os*; PSL, prednisolone.

Table 2 Treatment for acute exacerbation (AE) of interstitial pneumonia including direct haemoperfusion with a polymyxin B immobilized fibre column, and outcome in each of the five patients

Patient No.	Treatment for AE				PMX-DHP					Duration from AE (days)
	Steroid pulse therapy	Treatment after steroid pulse therapy	Cyclophosphamide pulse therapy	Mechanical ventilation	Commencing time from admission (days)	Commencing from the start of steroid pulse therapy (days)	Duration (h)	Number of cycles	Outcome	Cause of death	
1	+	sPSL 120 mg/day i.v.	+	+	3	3	3	2	died	AE of interstitial pneumonia	12
2	+	sPSL 120 mg/day i.v.	+	+	3	3	6	2	died	Pulmonary infection	23
3	+	sPSL 120 mg/day i.v.	+	+	3	3	6	2	died	Pulmonary infection	17
4	+	PSL 50 mg/day p.o.	–	–	2	0	12	2	improved	—	60
5	+	PSL 50 mg/day p.o.	–	–	0	0	12	2	improved	—	48

IIP, idiopathic interstitial pneumonia; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; PMX-DHP, direct haemoperfusion with a polymyxin B immobilized fibre column; p.o., *per os*; PSL, prednisolone; sPSL, soluble prednisolone.

(Fig. 1b). Patient 1 had IIP and was treated with two courses of 3 h each of PMX-DHP. Although the LDH level and WCC increased during PMX-DHP treatment (Fig. 1b,c), the P/F ratio rose markedly from 68 to 323 mm Hg (Fig. 1a) and the lung opacities seen on CXR improved immediately after PMX-DHP therapy (Fig. 2). However, 3 days later the P/F ratio decreased again to 33 mm Hg, and the patient died of respiratory failure 12 days after the onset of the acute exacerbation. The serum KL-6 level in this patient increased from 904 to 2220 U/mL despite PMX-DHP therapy. Patient 2 had MPO-ANCA-related interstitial pneumonia and Patient 3 had histologically proven IPF. These patients were given two courses of 6 h each of PMX-DHP. This therapy promptly raised their P/F ratio from 69 to 266 mm Hg, and from 59 to 300 mm Hg, respectively (Fig. 1a). Their CXR opacities improved (Case 2; Fig. 3) and serum LDH levels and WCC decreased (Fig. 1b,c). Although their P/F ratios remained at 150–200 mm Hg for 7–10 days, they eventually died from respiratory infections 17–23 days after the onset of the acute exacerbation. The serum KL-6 level decreased from 2300 to 1990 U/mL in Patient 2 and from 1300 to 699 U/mL in Patient 3 after PMX-DHP therapy. Patient 4 had clinical IPF and was given two courses of 12 h each of PMX-DHP. The P/F ratio increased gradually from 89 to 261 mm Hg over several days after PMX-DHP therapy (Fig. 1a). Patient 5 received two courses of 12 h each of PMX-DHP therapy, and the P/F ratio increased immediately from 195 to 322 mm Hg (Fig. 1a) with a reduction in serum LDH (Fig. 1b) and WCC (Fig. 1c). The lung opacities on CXR and HRCT also improved immediately after PMX-DHP treatment (Fig. 4). Patients 4 and 5 are still alive, more than 48 days after the onset of the acute exacerbation. The serum KL-6 level increased from 481 to 588 U/mL in Patient 4, and changed marginally from 2550 to 2590 U/mL in Patient 5. Cyclophosphamide pulse therapy was added, and mechanical ventilation was performed in patients 1–3. Sivelestat sodium hydrate was administered intravenously in patients 2 and 3.

Side-effects of PMX-DHP

Peripheral blood platelet levels decreased in four of five patients (patients 2–5) during PMX-DHP treatment. In patients 2 and 4, who developed disseminated intravascular coagulation (DIC), platelet levels decreased from an average of 228×10^9/L to 59×10^9/L. Patient 2 had massive bleeding from a gastric ulcer, possibly associated with the DIC, which developed 4 days after the onset of the acute exacerbation. Patient 4 did not have any severe complications other than respiratory failure, and the cause of DIC was unclear. In these two patients the platelet levels recovered following anticoagulant treatment. In patients 3 and 5, platelet levels decreased from an average of 163×10^9 to 115×10^9/L, and recovered spontaneously. No other side-effects were detected in any of the patients.

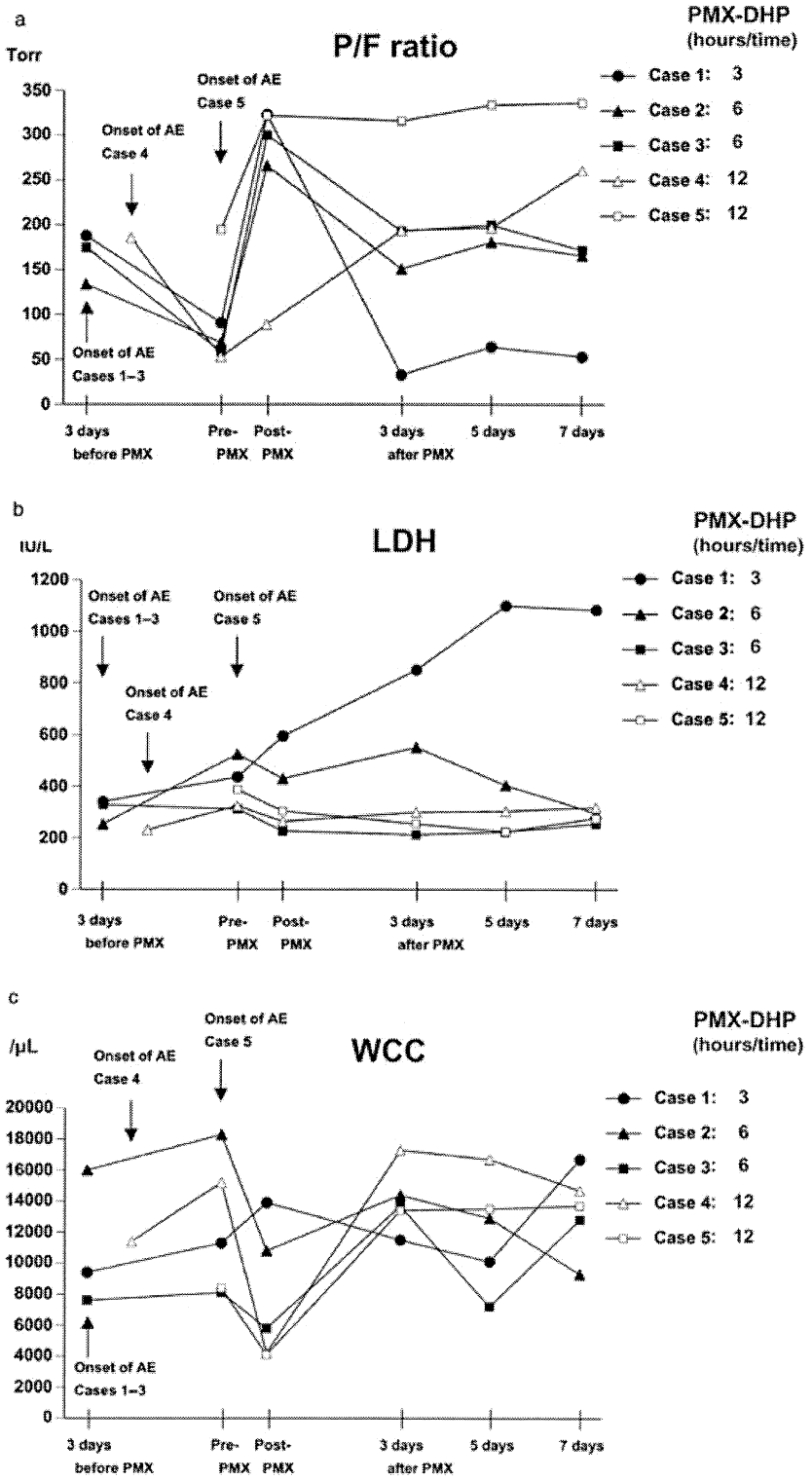

Figure 1 Kinetics of PaO_2/FiO_2 (P/F) ratio (a), serum LDH (b), and peripheral blood WCC (c) in five patients treated with direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP). PMX-DHP was administered for 3 h in Patient 1, 6 h in patients 2 and 3, and 12 h in patients 4 and 5.

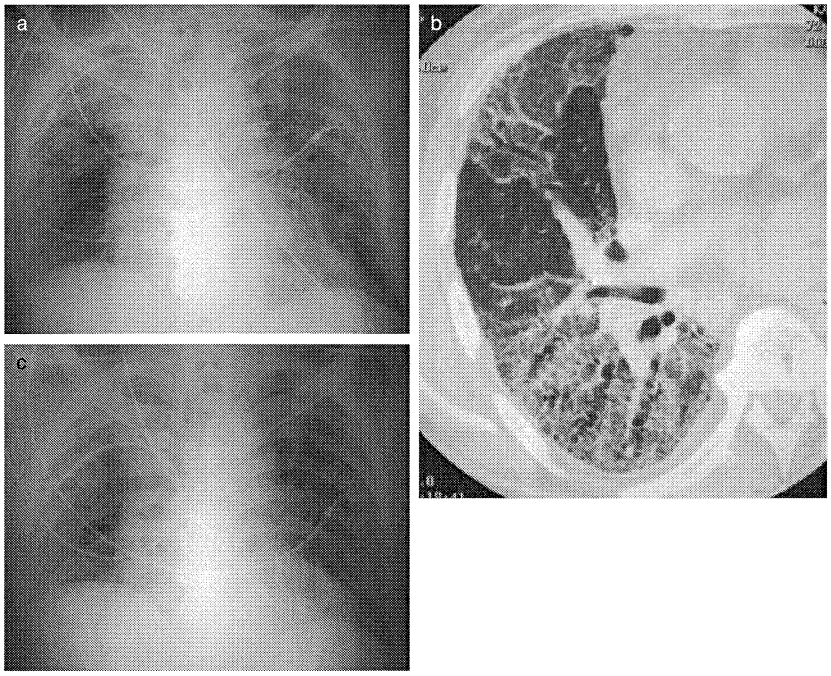

Figure 2 CXR and high-resolution CT (HRCT) of Patient 1, who was diagnosed with idiopathic interstitial pneumonia (IIP). Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (b) revealed bilateral diffuse ground glass opacities and reticular opacities, without honeycombing. He was treated with two courses of 3 h each of PMX-DHP together with corticosteroids and cyclophosphamide, and the lung opacities on his CXR improved immediately (c).

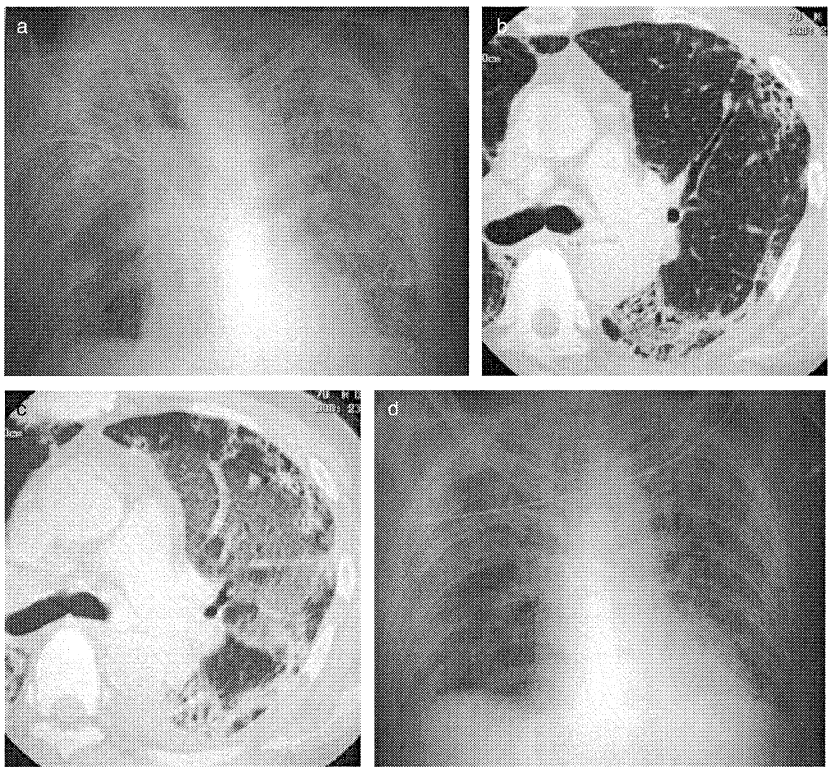

Figure 3 CXR and high-resolution CT (HRCT) of Patient 2, who was diagnosed with myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-related interstitial pneumonia. Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (c) revealed bilateral diffuse ground glass opacities and new reticular opacities. His HRCT just before the acute exacerbation (b) indicated the appearance of chronic interstitial pneumonia, such as traction bronchiectasis. He was treated with two courses of 6 h each of PMX-DHP together with corticosteroids and cyclophosphamide, and the lung opacities on his CXR improved immediately (d).

Kinetics of blood cytokines and high mobility group box protein 1

The serum levels of IL-6, IL-10, IL-8, neutrophil elastase and HMGB1, before and after PMX-DHP therapy were measured (Fig. 5). No significant changes were detected in the serum levels of cytokines, neutrophil elastase or HMGB1 in any of the patients. Three of the four patients who received 6- or 12-h courses of PMX-DHP (patients 2–5) showed a

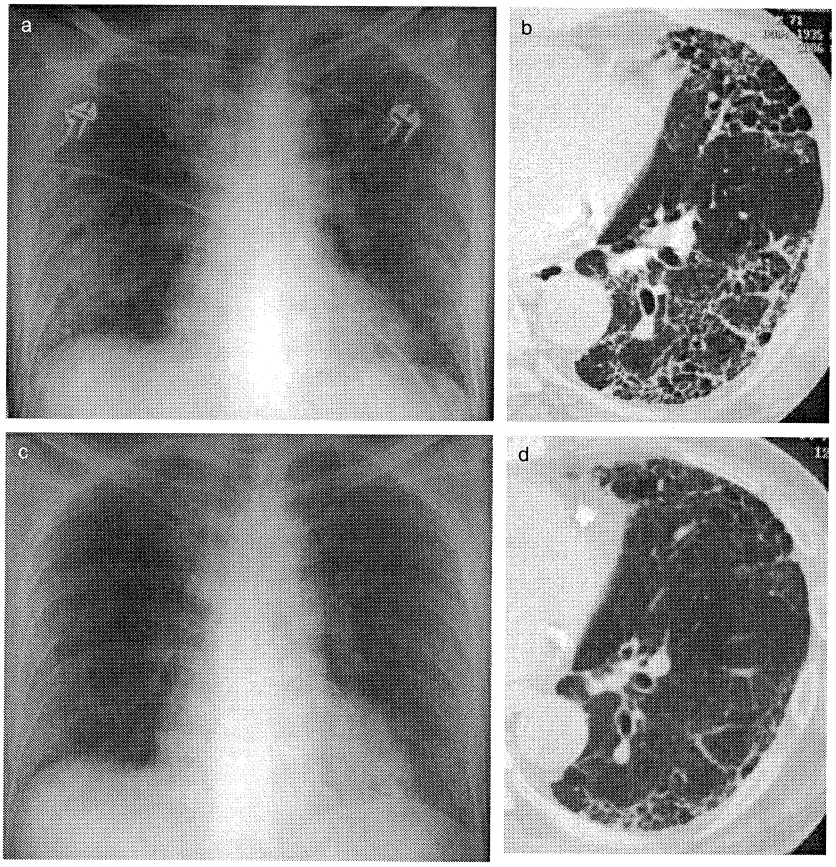

Figure 4 CXR and high-resolution CT (HRCT) of Patient 5, who was diagnosed with clinical IPF. Before direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP), his CXR (a) and HRCT (b) revealed ground glass opacities and reticular opacities, predominantly in the bilateral lower lobes. He was treated with two courses of 12 h each of PMX-DHP together with corticosteroids, and the lung opacities on his CXR (c) and HRCT (d) improved immediately.

decrease in serum IL-6 levels after therapy. IL-10 was not detected in the serum of any of the patients before or after PMX-DHP therapy.

DISCUSSION

The present study demonstrated that PMX-DHP dramatically improved pulmonary oxygenation in acute exacerbations of interstitial pneumonia, either with corticosteroids alone or plus cyclophosphamide, regardless of the aetiology and histology. However, three of five patients eventually died owing to respiratory failure or infection. PMX-DHP therapy appeared to be at least temporarily effective, and a longer duration (12 h) may give a better long-term outcome. Further study may elucidate the optimum method for administration of PMX-DHP for the treatment of acute exacerbations of interstitial pneumonia, such as the optimum duration and number of cycles.

Recently, Seo *et al.* demonstrated that PMX-DHP was an effective therapy for AE-IPF.[19] In that study, four of six patients treated with PMX-DHP showed a dramatic improvement in pulmonary oxygenation and were successfully weaned from mechanical ventilation, resulting in survival for longer than 30 days. However, no data were available on the effectiveness of PMX-DHP for the treatment of acute exacerbations of interstitial pneumonias other than IPF. In the present study, PMX-DHP with corticosteroids alone or plus cyclophosphamide also had a beneficial effect on pulmonary oxygenation in patients with non-IPF interstitial pneumonia. This suggests that PMX-DHP therapy can be used for the treatment of acute exacerbations of interstitial pneumonias with different aetiologies or histology. No serious adverse effects were observed during PMX-DHP therapy. Thrombocytopaenia occurred in four of five patients. Thus, PMX-DHP can safely be administered in patients with respiratory failure owing to an acute exacerbation of interstitial pneumonia.

The improvement in oxygenation with PMX-DHP typically occurred very rapidly. Patients showed a dramatic increase in P/F ratio during or just after PMX-DHP therapy. The improvement was striking in four patients (patients 1, 2, 3 and 5). In patients 1–3, the P/F ratios decreased further (to less than 100 mm Hg) before PMX-DHP, despite intensive therapy during this time. These patients usually do not respond well to any treatment, but PMX-DHP therapy led to a substantial improvement in their condition. On the other hand, oxygenation improved slowly following PMX-DHP treatment in Patient 4. Although the reason for this difference in the pattern of improvement is unclear, responsiveness may vary from patient to patient. With respect to long-term survival, three of the five patients eventually died of respiratory failure

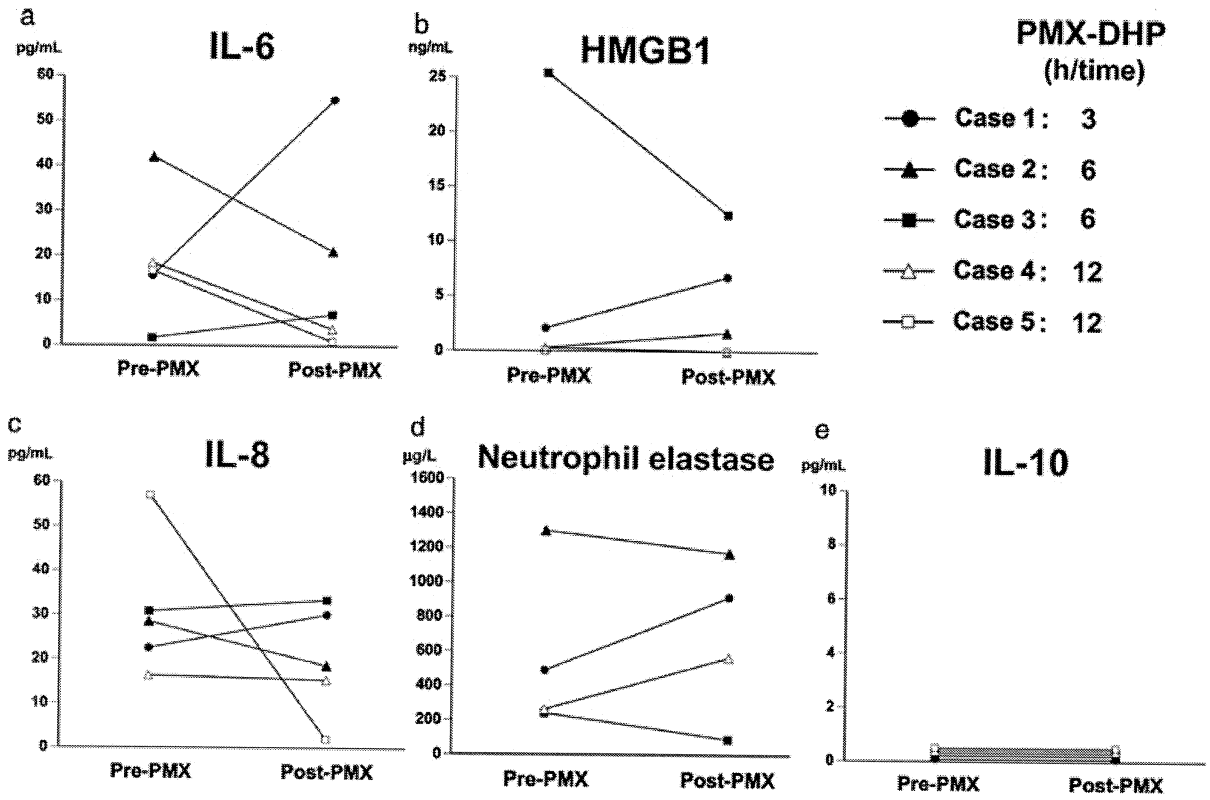

Figure 5 Kinetics of blood cytokines during direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP). (a) IL-6, (b) high mobility group box protein 1 (HMGB1), (c) IL-8, (d) plasma neutrophil elastase and (e) IL-10.

or infection, despite temporary improvements in pulmonary oxygenation after PMX-DHP with corticosteroids alone or plus cyclophosphamide. In contrast, Seo *et al.* reported that PMX-DHP increased pulmonary oxygenation and successfully saved four of six patients with AE-IPF.[19] In that study, two of the three AE-IPF patients with P/F ratios <110 mm Hg died of respiratory failure, whereas all three patients with P/F ratio > 180 mm Hg survived. This suggests that AE-IPF patients with severe respiratory failure do not respond well to PMX-DHP therapy. The P/F ratio was less than 100 mm Hg at the beginning of PMX-DHP therapy in four of the five acute exacerbation patients (Fig. 1a), which might account for their poor outcomes compared with those of the patients in the study of Seo *et al.*[19]

Although two courses of 2–3 h each of PMX-DHP therapy have been used for patients with sepsis,[13–15,17] the optimal duration and number of cycles remains to be determined for acute exacerbations of interstitial pneumonia. Seo *et al.* administered one to five courses of 2 h each in five patients, and 6 h each in another patient,[19] depending on the patient's condition. In the present study, Patient 1 was treated with two courses of 3 h each, but the therapeutic effect was temporary. Patients 2 and 3 were treated with two courses of 6 h each, and the effects lasted for 1–2 weeks. Patients 4 and 5 were treated with two courses of 12 h each, with persistent improvement in pulmonary oxygenation, and both survived. Thus, the longer courses of PMX-DHP appeared to be more effective, but further studies will be required to determine the optimum duration and number of cycles of PMX-DHP therapy in acute exacerbations of interstitial pneumonia.

To date, the mechanism by which PMX-DHP improves oxygenation in acute exacerbations of interstitial pneumonia is unclear. In the present study, PMX-DHP therapy did not significantly decrease the levels of IL-6, IL-8, IL-10, HMGB1 or neutrophil elastase in any patient. The peripheral blood WCC did, however, decrease during the 6 and 12 h courses of PMX-DHP (patients 2–5, Fig. 1c). It is possible that trapping of leukocytes, especially monocytes and neutrophils, within PMX-DHP columns may play an important role in its therapeutic effects. Recent studies have also reported that PMX-DHP reduced blood neutrophil elastase,[15] TNF-α,[21] matrix metalloproteinase-9, which enhances vascular permeability,[18] and intrapulmonary shunt ratio.[22] However, no significant decrease in blood neutrophil elastase was observed in the present study. Further studies are required to elucidate the precise mechanism by which PMX-DHP improves acute exacerbations of interstitial pneumonia.

There were several limitations to this study. First, the number of subjects was small. Second, because all patients treated with PMX-DHP were concurrently

treated with corticosteroids alone or plus cyclophosphamide, it is possible that the observed improvement in pulmonary oxygenation may not be attributable exclusively to PMX-DHP. Thus, further prospective controlled studies, with larger numbers of patients and a placebo group, will be required.

In conclusion, the present study demonstrated that PMX-DHP, either with corticosteroids alone or plus cyclophosphamide, significantly improved pulmonary oxygenation in acute exacerbations of interstitial pneumonia, regardless of the aetiology or histology, suggesting that this therapy has possible benefits in acute exacerbations that do not usually respond to intensive therapy and have an extremely poor outcome. The main limitation of this study was the small number of patients. Therefore, the most effective way to administer PMX-DHP, and the long-term outcome, will need to be further defined in a larger series of patients.

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