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Direct Hemoperfusion Using Immobilized Polymyxin B in Patients with Rapidly Progressive Interstitial Pneumonias: A Retrospective Study

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Key Words
Rapidly progressive interstitial pneumonia · Acute exacerbation · Polymyxin B direct hemoperfusion · Monocyte chemotactic protein 1 · Arterial oxygen tension/inspiratory oxygen fraction ratio

Abstract
Background: Rapidly progressive interstitial pneumonia (IP), including acute exacerbation of IP, has a high mortality rate. Direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) was recently identified as an effective treatment for sepsis-associated acute respiratory distress syndrome. However, little is known about the effectiveness of PMX-DHP for rapidly progressive IP. ***Objectives:*** The present study investigates whether PMX-DHP is safe and effective against rapidly progressive IP. ***Methods:*** We retrospectively examined the effects of PMX-DHP in 33 consecutive patients with rapidly progressive IP who were resistant to steroid pulse therapy. Patients were hospitalized at Nagasaki University Hospital between 2006 and 2009. ***Results:*** Seventy-two hours after PMX-DHP, the arterial oxygen tension/inspiratory oxygen fraction ratio (median 127–153 mm Hg) had significantly improved. One week after PMX-DHP, the arterial oxygen tension/inspiratory oxygen fraction ratio (median 127–227 mm Hg), the alveolar-arterial difference of oxygen (median 371–177 mm Hg) and the number of positive criteria for systemic inflammatory response syndrome had significantly improved, despite the ineffectiveness of corticosteroid pulse therapy. The serum level of monocyte chemotactic protein 1 was significantly decreased immediately after PMX-DHP. ***Conclusions:*** PMX-DHP was safe and effective in improving oxygenation and systemic inflammatory response syndrome in patients with rapidly progressive IP. The beneficial effects of PMX-DHP may be at least partially due to the inhibition of monocyte activation.

Introduction

Direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) has been used to treat sepsis by removing endotoxins produced by Gram-negative bacteria [1]. A recent multi-center randomized controlled trial confirmed that PMX-DHP is more effective than conventional therapy in patients with sepsis [2] and

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indicated that PMX-DHP might favorably affect endotoxin levels, arterial blood pressure, vasopressor requirement, the arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) ratio (P/F) and mortality. Studies have also found that PMX-DHP is helpful for patients with complicated acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), which is pathologically characterized by diffuse alveolar damage (DAD) [3–6]. DAD is also evident in some patients with rapidly progressive interstitial pneumonia (IP). The course of rapidly progressive IP is quick, the diagnostic modalities are suboptimal, and the outcomes are poor. In the present study, we define rapidly progressive IP as interstitial lung disease with acute to subacute respiratory failure, with bilateral infiltrative shadows on chest high-resolution computed tomography, and no known alternative causes of ALI (such as pneumonia, sepsis, trauma, toxic inhalation, blood infusion, acute pancreatitis, thromboembolism, or heart failure). Rapidly progressive IP includes idiopathic acute IP and IP with clinically amyopathic dermatomyositis [7–9]. Acute IP is a rapidly progressive condition of unknown cause that occurs in a previously healthy individual and produces the histologic findings of DAD [10]. Because of its acute presentation and histologic features similar to those of ARDS, acute IP is considered to be an idiopathic form of ARDS [10, 11]. In addition, patients with chronic IP sometimes rapidly deteriorate. This phenomenon is called 'acute exacerbation of IP' (AE-IP). Kondoh et al. [12] originally described AE-IP in patients with idiopathic pulmonary fibrosis. AE also occurs in idiopathic nonspecific IP, IP associated with connective tissue diseases, chronic hypersensitivity pneumonitis, and pneumoconiosis [13–16]. In this study, rapidly progressive IP also includes patients with AE-IP. Such patients are often resistant to intensive therapy, resulting in a fulminant and devastating course, with mortality rates ranging from 50 to 90% [7, 14, 17]. Therefore, novel effective therapies for these rapidly progressive and fatal lung diseases are needed. A few small study reports indicate that PMX-DHP could be a promising treatment candidate [18–21]. The effects, safety and applicability of PMX-DHP against rapidly progressive IP remain unknown. Furthermore, the mechanisms responsible for improved oxygenation after PMX-DHP have not been elucidated. To clarify the effectiveness and safety of PMX-DHP, we reviewed 33 consecutive patients with rapidly progressive IP. In addition, to elucidate the mechanism of effectiveness, we evaluated changes in serum chemokines associated with acute inflammation and lung injury, such as monocyte chemotactic protein 1 (MCP-1).

Patients and Methods

Patients

The Human Ethics Review Committees of Nagasaki University Hospital approved the study protocol. All participants or their families provided written, informed consent for all study procedures. Thirty-three consecutive patients with rapidly progressive IPs were enrolled in an open-label pilot trial of PMX-DHP at Nagasaki University Hospital between 2006 and 2009. Patients who met the following criteria were diagnosed with rapidly progressive IP: (1) development or unexplained worsening of dyspnea within 30 days; (2) high-resolution computed tomography with new bilateral ground-glass opacities and/or consolidation; (3) stable P/F ratio <300 mm Hg; and (4) absence of apparent infection, pneumothorax, pulmonary thromboembolism, heart failure or alternative causes of acute lung injury, such as trauma, blood infusion or toxic inhalation. Serological and urinary studies for the following pathogens and pathogen components were negative in all patients: endotoxin, *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydophila psittaci,* cytomegalovirus antigenemia and β-D-glucan (for *Pneumocystis jiroveci* pneumonia), *Legionella* spp. and *Streptococcus pneumoniae.* Blood, sputum and urine cultures were also negative. Echocardiography demonstrated no evidence of heart failure in any of the patients.

The 33 study patients fulfilled our criteria (described above) for rapidly progressive IP; however, the patient group had varied etiologies. Effectiveness and prognosis could be influenced by underlying diseases and clinical course or treatment, especially mechanical ventilation. However, because of the small study population, the compartmentalization of diseases would make the statistical analysis difficult. Therefore, for our analysis, we separated the patients into 2 subgroups based on the presence or absence of idiopathic IP (IIP), which was diagnosed according to the classification system of the American Thoracic Society/European Respiratory Society [22]. The non-IIP group included patients with connective tissue disease-associated IP (underlying autoimmune diseases or vasculitis), drug-induced lung disease, pneumoconiosis and chronic hypersensitivity pneumonitis. Some patients had received bronchoalveolar lavage and surgical lung biopsy for the diagnosis of IP before the onset of rapidly progressive IP.

Procedure

We administered PMX-DHP to patients who were resistant to standard treatments for rapidly progressive IP, including high-dose corticosteroid pulse therapy (methylprednisolone 1,000 mg/day). The prednisolone dosage was tapered after high-dose corticosteroid pulse therapy, and immunosuppressants were also prescribed for some patients. Several reports have indicated that antioxidant therapy, such as N-acetylcysteine [23–25] or anticoagulation therapy [26–28], is useful for ALI/ARDS; however, none of the study patients received antioxidant or anticoagulation therapy.

PMX-DHP (Toraymyxin, Toray Medical Co., Tokyo, Japan) was performed with conventional equipment and a circuit for hemodialysis. A double-lumen catheter was inserted into the femoral vein for venous access, and patients were directly hemoperfused at a flow rate of 80–100 ml/min for 3–24 h. Each patient received 1–6 treatments with PMX-DHP. Nafamostat mesylates (Torii Pharma Co. Ltd., Tokyo, Japan) were used as anticoagulants. We had no standard therapeutic criteria for the duration

and number of PMX-DHP sessions; rather, we used the process of trial and error to determine the duration and number of PMX-DHP sessions. The timing of administration, duration, number of cycles and time delay of each cycle were not unified and depended upon the assessment of the attending physician in each case. In a similar fashion, we had no standard ventilation strategy. The timing of intubation, duration, ventilation mode and ventilating parameters (including positive end-expiratory pressure level, tidal volume, airway pressure and respiratory rate) varied and depended on the assessment of the attending physicians.

Data Collection and Management

Clinical data were recorded at baseline (just prior to the first PMX-DHP session) and at 72 h and 1 week after the initial PMX-DHP session. To evaluate the disease severity, we used the Acute Physiology and Chronic Health Evaluation (APACHE) II score (range 0–35; higher scores predict severe mortality) [29] and the Sequential Organ Failure Assessment (SOFA) score (range 0–24; lower scores indicate better organ function) [30]. The delta SOFA [31–33], which was calculated as the SOFA score at each time point minus the SOFA score at baseline, was used to determine the change in the degree of organ dysfunction after the 1st PMX-DHP session. The Glasgow Coma Scale of patients who underwent mechanical ventilation (MV) was assumed to be 3 points. The APACHE II score was assessed just prior to the first PMX-DHP. Furthermore, we assessed whether patients fulfilled the systemic inflammatory response syndrome (SIRS) criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference [34, 35]. The P/F ratio and alveolar-arterial oxygen difference (A-a DO_2) were approximated by the following expectation values of FiO_2 in patients without MV: room air = 0.21; nasal cannula: 1 l/min = 0.24, 2 l/min = 0.28, 3 l/min = 0.32, 4 l/min = 0.36, 5 l/min = 0.40; mask: 5 l/min = 0.40, 6 l/min = 0.50, 7 l/min = 0.60; reservoir mask: 6 l/min = 0.60, 7 l/min = 0.70, 8 l/min = 0.80, 9 l/min = 0.90, and 10 l/min = 0.99. PaO_2 and arterial carbon dioxide tension were measured by the analysis of arterial blood gas in all cases.

Endpoints

The primary endpoint was the change in the P/F ratio from baseline (just prior to the 1st PMX-DHP session) to 72 h after the 1st PMX-DHP, which is the same primary endpoint as used in the EUPHAS trial [2]. The secondary endpoints included the change in the P/F ratio from baseline to 1 week, changes in the A-a DO_2, the number of positive SIRS criteria, the change in SOFA score from baseline to 72 h or 1 week after the 1st PMX-DHP, and the 30- and 90-day mortality.

Assessment of Safety

To clarify the safety of PMX-DHP, we investigated body temperature, mean blood pressure, heart rate, respiratory rate, white blood cell and platelet count in all patients at baseline, 72 h and 1 week after the 1st PMX-DHP session.

Measurement of Chemokines

Blood samples were taken just before and after each PMX-DHP treatment. The serum levels of MCP-1, interleukin (IL)-8, granulocyte colony-stimulating factor, growth-regulated peptide α, epithelial neutrophil-activating peptide 78 and plasma levels of stromal cell-derived factor 1α were measured using ELISA kits. The MCP-1 ELISA kit was from Bender MedSystems GmbH (Vienna, Austria), and all other kits were from R&D Systems, Inc. (Minneapolis, Minn., USA). Blood samples were preserved by freezing and measured retrospectively. However, we could not collect blood samples in all cases, and some samples were not large enough to measure all chemokines. MCP-1 was measured in 51 cycles from 21 cases, and the other chemokines were measured in 20 cycles of 11 cases.

Statistical Analysis

Values are expressed as medians and interquartile ranges (IQRs) for continuous parameters. All statistical analyses were performed with SAS® (version 9.1, SAS Institute Inc., Cary, N.C., USA). We compared changes in the P/F ratio, A-a DO_2, SIRS items, SOFA score, vital signs and other laboratory data between baseline and 72 h or 1 week after the first PMX-DHP session using the Wilcoxon test. We performed comparisons between the 2 subgroups, IIP and non-IIP, using a general linear model for repeated measures. We used the general linear model and NPAR1WAY in the SAS system for the calculations. Interactions between subgroups and time were also evaluated. Differences in mortality between the 2 subgroups were compared using the log-rank test. p values <0.05 were considered statistically significant, and all tests were 2-tailed.

Results

Clinical Features of Patients

The clinical characteristics of all patients are shown in table 1. Thirty-three patients (18 men and 15 women) with a median age of 69 years (IQR 63–74) received a total of 73 cycles of PMX-DHP. Patients were classified into 2 subgroups, the IIP subgroup (n = 17) and the non-IIP subgroup (n = 16).

One patient (No. 22) was diagnosed with inflammatory myopathy with abundant macrophages based on the infiltration of CD68+ macrophages into the biopsied specimens, especially the fascia. Proximal skeletal muscle symptoms and signs, elevation of creatine kinase and myogenic changes in electromyography were present, but dermatomyositis-specific skin alterations were absent. One of the clinically amyopathic dermatomyositis patients (No. 23) has been described in a case report [20]. Drug-induced lung disease was suspected in 3 patients who received biapenem (No. 26), docetaxel (No. 27) or crude drug extract (Mitakesan-Fudogan®; No. 28). Itraconazole-induced diffuse alveolar hemorrhage was suspected in patient No. 29, who has been described in a case report [36]. Eight patients were pathologically diagnosed by video-assisted surgical lung biopsy before the onset of rapidly progressive disease. Five patients had been diagnosed with clinical idiopathic pulmonary fibrosis without surgical lung biopsy according to the international

Table 1. Clinical characteristics

Patient No.	Sex	Age years	Subgroup	Diagnosis	Duration of underlying disease years	Histo-patho-logical diagnosis	Previous therapy	MV		
								intuba-tion	commencing from admis-sion, days	dura-tion days
1	F	63	IIP	IPF, AE	2	UIP	PSL+CPA	+	3	45
2	F	61	IIP	IPF, AE	8	UIP	PSL+CPA	–		
3	F	81	IIP	IPF, AE	7	UIP	–	+	1	7
4	M	68	IIP	IPF, AE	1	UIP	–	–		
5	M	69	IIP	IPF, AE	2	–	PSL+CyA	+	7	20
6	M	71	IIP	IPF, AE	2	–	–	–		
7	M	49	IIP	IPF, AE	5	–	NAC	–		
8	M	56	IIP	IPF, AE	4 months	–	pirfenidone	–		
9	M	58	IIP	IPF, AE	3	–	PSL	+	9	15
10	M	67	IIP	NSIP, AE	3	NSIP	–	+	2	24
11	M	67	IIP	unclassified IP, AE	1	–	–	+	2	4
12	F	75	IIP	idiopathic AIP	–	–	–	NPPV	1	11
13	M	79	IIP	idiopathic AIP	–	–	–	+	2	57
14	M	69	IIP	idiopathic AIP	–	–	–	–		
15	F	65	IIP	idiopathic AIP	–	–	–	+	6	25
16	F	47	IIP	idiopathic AIP	–	–	–	+	0	14
17	F	81	IIP	idiopathic AIP	–	–	–	+	3	77
18	F	70	non-IIP	RA, AE	18	UIP	PSL+CyA	NPPV	2	3
19	F	74	non-IIP	RA, DM, SjS, AE	15	UIP	PSL+mizoribine	+	3	4
20	F	72	non-IIP	primary SjS, AE	3	–	–	+	3	5
21	M	74	non-IIP	systemic vasculitis, AE	1	–	–	–		
22	F	46	non-IIP	IMAM, ARS	–	–	–	–		
23	M	70	non-IIP	CADM	–	–	–	+	2	8
24	F	60	non-IIP	CADM	–	–	–	–		
25	F	69	non-IIP	CADM	–	–	–	–		
26	M	85	non-IIP	drug-induced IP	–	–	–	+	3	82
27	F	69	non-IIP	drug-induced IP	–	–	–	NPPV	11	3
28	M	82	non-IIP	drug-induced IP	–	–	–	+	2	21
29	M	53	non-IIP	drug-induced alveolar hemorrhage	–	–	–	+	0	5
30	F	75	non-IIP	asbestosis, AE	10	–	PSL	–		
31	M	82	non-IIP	asbestosis, AE	30	–	–	–		
32	M	69	non-IIP	asbestosis, AE	2	–	–	+	4	15
33	M	65	non-IIP	chronic HP, AE	2	NSIP	–	–		

Histopathological diagnosis was revealed by surgical lung biopsy before the onset of rapidly progressive IP. All patients were treated with oral or intravenous corticosteroids after high-dose corticosteroid pulse therapy.

CyA = Cyclosporin A; IPF = idiopathic pulmonary fibrosis; UIP = usually interstitial pneumonia; PSL = prednisolone; CPA = cyclophosphamide; NAC = inhalation of N-acetylcysteine; NSIP = non-specific interstitial pneumonia; AIP = acute interstitial pneumonia; NPPV = non-invasive positive airway pressure ventilation; RA = rheumatoid arthritis; DM = dermatomyositis; SjS = Sjögren syndrome; IMAM = inflammatory myopathy with abundant macrophages; ARS = anti-aminoacyl tRNA synthetase syndrome; CADM = clinically amyopathic dermatomyositis; TA = tacrolimus; HP = hypersensitivity pneumonia.

[1] Tacrolimus, cyclophosphamide, leukocytapheresis and plasmapheresis (case No. 22).

consensus statement of the American Thoracic Society/European Respiratory Society [22]. Six patients received corticosteroid therapy before onset; four of these patients underwent immunosuppressive therapy with cyclophosphamides (n = 2), cyclosporin (n = 1) or mizoribine (n = 1). One patient received inhalation therapy with N-acetylcysteine, and 1 patient pirfenidone. PMX-DHP treatment was commenced after a median of 5 days (IQR 3.0–6.0) from admission and 3 days (IQR 2–5) from the start of corticosteroid pulse therapy. The median number of

PMX-DHP					Treatment		Outcome	Survival (from 1st PMX-DHP) days
commencing from admission days	starting from steroid pulse therapy, days	cycles	duration h	time delay between each cycle, days	CyA	others		
7	4	3	4	2, 5	+		dead	41
5	5	2	4	1	+		alive	
2	2	2	3	1	+		dead	13
4	4	2	8.5	1	+		alive	
6	6	4	4	2, 2, 2	+		dead	22
6	0	6	4	2, 4, 1, 8, 1	+		dead	25
4	4	3	6	2	+		dead	75
6	6	2	6	2	+		alive	
9	1	2	19	2	–		dead	15
5	4	2	4	1	+		alive	
3	3	1	4	–	–		alive	
1	1	4	4	3, 3, 4	+	CPA	dead	11
2	2	4	4	2, 6, 6	+		dead	57
3	2	2	6	1	+		alive	
6	4	2	4	2	+		dead	25
9	9	2	6	1	-		dead	14
3	3	1	18	–	+		dead	79
2	2	2	4	2	+		alive	
4	2	1	6	–	+		dead	20
3	2	2	3	1	–		alive	
4	4	2	6	1	–	CPA	alive	
2	1	1	4	–	–	–[1]	alive	
7	5	2	3	1	+		alive	
17	16	2	3	1	+		alive	
18	11	3	4	5, 15	+	CPA, TA	dead	24
6	3	2	4	1	+		alive	
12	12	2	6	2	–		dead	7
6	5	2	4	1	+		dead	58
2	2	1	24	–	–		alive	
2	2	2	4	2	–		dead	21
8	8	2	4	2	+		alive	
3	3	1	6	–	–		dead	16
5	2	2	4	1	+		alive	

cycles was 2 (IQR 2–2), and the median duration was 4 h (IQR 4–6). Twenty patients received MV (17 intubated and 3 noninvasive positive-airway pressure ventilations) by 1 week after the initial PMX-DHP treatment. The ventilation was commenced at a median of 2.5 days (IQR 2.0–3.3) after admission, and the median duration was 14.5 days (IQR 5.0–24.3). Of the 17 patients who died, 13 underwent mechanical ventilation, and 5 of them had been weaned from it once. However, they eventually died from the exacerbation of respiratory failure or infection

Table 2. Clinical course of laboratory data and vital signs

Value	Baseline			72 h				1 week			
	median	IQR	n	median	IQR	n	p value	median	IQR	n	p value
P/F ratio, mm Hg	127.0	91.1–150.9	33	152.8	116.5–274.4	33	0.02	226.7	138.2–307.6	33	0.0004
A-a DO_2, mm Hg	370.6	173.2–430.2	33	278.7	138.5–418.7	33	NS	177.2	61.1–299.2	33	0.0014
Positive SIRS criteria	2	1–2	30	1	1–2	30	0.06	1	0–2	30	0.04
SOFA score	4	3–8.5	28	5	3–9	27	NS	4	2–8	27	NS
Body temperature, °C	36.7	36.4–37.0	31	36.6	36.5–36.9	31	NS	36.6	36.4–36.8	31	NS
Mean blood pressure, mm Hg	90	79.3–100.7	31	89	78.7–96.0	30	NS	89	77.3–96.7	30	NS
Heart rate, beats/min	84	71–100	31	78	60–86	31	0.09	76	60–88	31	NS
Respiratory rate, beats/min	24	20–30	31	20	20–28	31	0.03	22	20–30	31	0.08
White blood cell, $10^3/\mu l$	12,300	9,900–16,900	32	9,400	7,600–12,900	30	0.01	10,250	9,000–15,700	30	NS
Platelet count, $10^4/\mu l$	18.7	12.8–25.0	30	14.0	10.1–19.0	30	0.05	17.3	11.4–24.0	30	NS

Comparisons between baseline and 72 h or 1 week were performed with the Wilcoxon test. Values are expressed as medians and IQRs (25–75%). NS = Not significant.

Table 3. Subgroup comparisons (IIP vs. non-IIP)

	p value		
	between subjects (subgroup)	within subjects (time)	subject-time interaction
P/F ratio	0.03	<0.0001	0.07
A-a DO_2	0.09	0.0001	NS
SIRS	NS	0.002	NS
SOFA	NS	NS	NS

Thirty-three patients were divided into 2 subgroups: IIP and non-IIP. The comparisons between the 2 subgroups were calculated by a general linear model for repeated measures in the SAS system. NS = Not significant.

including *P. jiroveci* pneumonia, cytomegalovirus pneumonia and multidrug-resistant *Pseudomonas aeruginosa* pneumonia. Pathological assessments of 3 patients (No. 1, 3 and 12) at autopsy confirmed that they had DAD.

Primary Endpoints

The P/F ratio among the entire patient group significantly improved from baseline to 72 h after the 1st PMX-DHP session (table 2; fig. 1a). However, improvement in the P/F ratio at 72 h among patients in each subgroup was not statistically significant (fig. 1b).

Secondary Endpoints

The P/F ratio and A-a DO_2 among the entire patient group significantly improved from baseline to 1 week after the 1st PMX-DHP session (table 2; fig. 1a, Wilcoxon test). The number of patients who fulfilled SIRS criteria decreased from 16 of 31 (at baseline) to 11 of 30 (at 72 h) and to 10 of 30 (at 1 week); however, these changes were not statistically significant as determined by the χ^2 test. On the other hand, the number of positive SIRS criteria was significantly decreased 1 week after treatment (table 2). The SOFA score showed no significance overall (table 2). A between-subgroup comparison performed with the general linear model for repeated measures revealed that the P/F ratio showed statistical significance (table 3). But none of the items showed a significant interaction between subgroup and time.

Thirty-day mortality was 36.4% (12 of 33 patients), and 90-day mortality was 51.6% (17 of 33 patients). The median survival duration was 27 days (IQR 19–48) from admission and 22 days (IQR 15–41) from the 1st PMX-DHP treatment. In subgroup comparisons performed with the log-rank test, the 30- and 90-day mortality was 41.2 (7 of 17) and 64.7% (11 of 17) for the IIP subgroup and 31.3 (5 of 16) and 37.5% (6 of 16) for the non-IIP subgroup, respectively (p = 0.18).

Safety and Adverse Reactions

To clarify the safety of PMX-DHP, we investigated the clinical course of the vital signs and laboratory data (table 2). Patient vital signs did not deteriorate during PMX-DHP treatment, and no patient required additive vasopressor. White blood cell counts significantly decreased 72 h after the 1st PMX-DHP session, but they remained increased 1 week after the 1st PMX-DHP session. Platelet

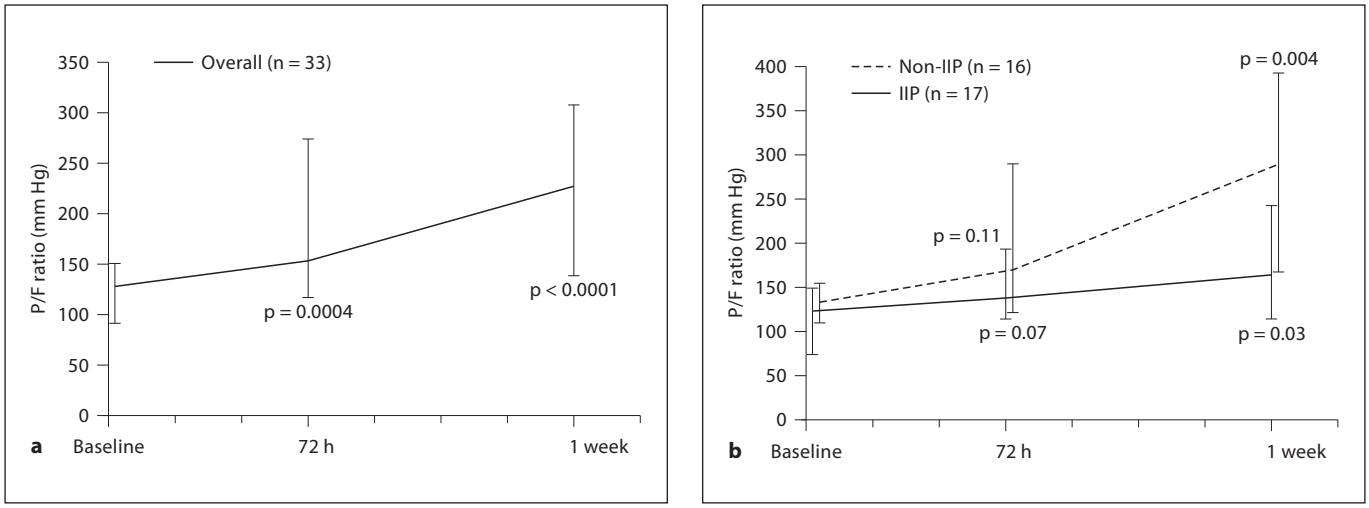

Fig. 1. Clinical course of P/F ratio. The statistical analysis was performed with the Wilcoxon test. The p values indicate the comparisons with baseline values. Values are expressed as medians and IQRs (25–75%). **a** Overall. **b** Subgroup comparison.

Table 4. Changes in chemokines

Chemokines	Pre-PMX-DHP		Post-PMX-DHP		Sessions	p value
	median	IQR	median	IQR		
MCP-1	637	494–1,193	460	375–893	51	<0.001
IL-8	38.8	30.4–50.7	40.5	32.1–57.3	20	NS
GROα	64.5	52.0–90.8	56.6	46.9–68.9	20	0.08
ENA-78	289	233–542	290	158–481	20	NS
SDF-1α	2,314	2,028–2,579	2,374	2,002–2,575	20	NS

Statistical analysis was performed with the Wilcoxon's signed rank test. Values are expressed as medians and IQRs. NS = Not significant; GROα = growth-regulated peptide α; ENA-78 = epithelial neutrophil-activating peptide 78; SDF-1α = stromal cell-derived factor 1α.

counts also significantly decreased at 72 h but recovered 1 week after the 1st PMX-DHP session. None of the patients showed a tendency to bleed or required a blood transfusion during PMX-DHP. The serum levels of C-reactive protein obviously decreased during the clinical course. However, the serum levels of lactate dehydrogenase, blood urea nitrogen, creatinine, sodium and potassium were not affected by PMX-DHP (data not shown).

Chemokines

Serum levels of MCP-1 were significantly decreased immediately after PMX-DHP as compared with baseline levels ($p < 0.001$) (table 4). The levels of MCP-1 decreased significantly in both the survivor group (median 590–399; $p = 0.003$) and the non-survivor group (median 642–466; $p = 0.02$), and no significant difference was observed between the 2 groups. Serum levels of IL-8, growth-regulated peptide α, epithelial neutrophil-activating peptide 78 and stromal cell-derived factor 1α were not significantly affected.

Discussion

Our results indicate that PMX-DHP offers promise as a safe and effective therapy for rapidly progressive IP of different etiologies that is resistant to initial corticosteroid pulse therapy. This study is the first retrospective

investigation of more than 30 patients with rapidly progressive IP. We found that PMX-DHP improved oxygenation at 72 h and SIRS criteria at 1 week after the 1st PMX-DHP session. The improved oxygenation occurred in both the IIP subgroup and the non-IIP subgroup. Also, the serum levels of MCP-1 were decreased just after PMX-DHP; this decrease may precede the enhancement of oxygenation.

Rapidly progressive IP is a very complex and severe disease, and it requires intensive therapy. The major finding in the present study is that PMX-DHP rapidly improved oxygenation in patients whose oxygenation had deteriorated despite initial corticosteroid pulse therapy. Of the 17 patients who died, 13 patients underwent mechanical ventilation. Five ventilated patients were weaned from the ventilation at one point. Our findings are consistent with other reports that have described the effectiveness of PMX-DHP for patients with AE-IP [18, 19, 21]. In addition to our assessment of oxygenation, we also assessed the systemic effect of PMX-DHP on rapidly progressive IP. PMX-DHP has been reported to affect endotoxin levels, arterial blood pressure, vasopressor requirements and the P/F ratio. These reports indicated that PMX-DHP has a beneficial effect on rapidly progressive IP by not only improving oxygenation but also by regulating the patient's systemic status. In the present study, the number of patients who fulfilled SIRS criteria decreased after PMX-DHP. Likewise, the number of positive SIRS criteria was significantly decreased 1 week after the 1st PMX-DHP session. SIRS, which is a systemic host response to infection and other forms of tissue injury, reflects changes in thermoregulation, the emergence of cardiovascular and respiratory instability, and alterations in white blood cell count [34, 35]. SIRS progresses to ALI/ARDS, whereas rapidly progressive IP also progresses to SIRS and multiple organ dysfunctions. Assessment of SIRS criteria in patients with rapidly progressive IP could identify other benefits of PMX-DHP. A recent randomized controlled study showed that PMX-DHP improved SOFA scores and the mortality rate of patients with sepsis [2]. However, in the present study, the SOFA score was not affected by PMX-DHP. Other scoring systems could be useful to assess patients with IP; for example, the RIFLE score predicts the outcome of ARDS patients who undergo open lung biopsy [37]. The mortality rates for patients with rapidly progressive IP in 3 recent reports [18, 19, 21] were 33.3, 50 and 60%, respectively. The 30-day mortality rate in the present study was 36.3%, and the 90-day mortality rate was 51.6%. Rapidly progressive IP has an extremely poor prognosis, and the initial treatment at the acute stage is important. For these reasons, we have emphasized the short-term effects of PMX-DHP and included 30- and 90-day mortality as secondary endpoints. Although the length of the final observation period varied from 1 to 4 years because of the retrospective nature of the study, the 90-day morality rate was the same as the mortality rate at the final observation period. Re-exacerbation of respiratory failure or infection should be prevented during the clinical course to decrease the final mortality rate. Because this study is a retrospective cohort study, whether or not PMX-DHP can reduce mortality remains unknown. Although the transient improvement in oxygenation did not ensure a good prognosis, the improved oxygenation could preserve lung tissue from oxygen toxicity, reduce the duration of mechanical ventilation and provide an opportunity for other intensive therapies to work.

The patients with rapidly progressive IP in the present study formed a heterogeneous population with different underlying diseases and therapies other than PMX-DHP. To discover the population that responded to PMX-DHP, we divided the patients into 2 subgroups (IIP or non-IIP) based on the underlying IP. The oxygenation and SIRS criteria were improved by PMX-DHP in both subgroups. Although the P/F ratio at 1 week after the 1st PMX-DHP session in the non-IIP group was significantly higher than in the IIP group, no significant interaction between subgroup and time was observed. The 30- and 90-day mortality was not significantly different between the 2 subgroups.

When we attempt new treatment methods, it is important to assure that the methods are safe, especially for severe cases. In the present study, the patients' vital signs were stabilized, and there were no adverse reactions or changes in laboratory data, except for mild thrombocytopenia. Furthermore, there have been no reports that PMX-DHP reduces the in vivo efficiency of treatment with steroids or immunosuppressants. Thus, PMX-DHP can be safely administered to patients with rapidly progressive IP.

The mechanisms by which PMX-DHP improves oxygenation in rapidly progressive IP remain unclear. Here, we found that the serum levels of MCP-1 after PMX-DHP were significantly decreased as compared with the levels before PMX-DHP treatment. MCP-1 is produced by a variety of cells including monocytes. It belongs to the CC subgroup (β subfamily) of the chemokine superfamily [38] that plays a critical role in the recruitment and activation of monocytes during acute inflammation [39]. On the other hand, serum levels of IL-8, growth-regulated

peptide α, stromal cell-derived factor 1α and epithelial neutrophil-activating peptide 78 were not affected. These mediators belong to the CXC family (α subfamily) that selectively attracts neutrophils. The MCP-1 levels in bronchoalveolar lavage fluid and sera in patients with idiopathic pulmonary fibrosis and other types of IP are increased [40–42]; likewise, increased levels of CXC chemokines are associated with pathological conditions in IP [43–45]. The blood levels of some inflammatory chemokines, e.g. metalloproteinase 9, tissue inhibitor of metalloproteinase 1 [4], neutrophil elastase, IL-8 [46] and IL-18 [47], are immediately decreased in ARDS patients after PMX-DHP. Seo et al. [18] have reported that IL-6, IL-8 and plasminogen activator inhibitor 1 are decreased in patients with rapidly progressive IP who responded to PMX-DHP. Noma et al. [19] have reported that high mobility group box 1, MCP-1, IL-6 and IL-8 are reduced 72 h after PMX-DHP. Our results indicate that MCP-1 itself or MCP-1-producing cells including monocytes may be absorbed by PMX-DHP. Kushi et al. [48] have shown that PMX-DHP decreases macrophage and monocyte activity, and Nishibori et al. [49] have used immunocytochemical and microscopic techniques to demonstrate that PMX-DHP binds to monocytes. Although it is unclear whether the reduction of such chemokines has direct or indirect effects, the decreasing MCP-1 levels might partially explain the benefits of PMX-DHP. The measurement of chemokines along with clinical courses may provide new insights, and further studies are required to elucidate the precise mechanisms responsible for the beneficial effects of PMX-DHP.

The present study has a number of limitations. The study cohort was small, the design was retrospective, and the pathological findings were unclear in most patients. In addition, the etiologies, the underlying diseases and treatments, the number and durations of PMX-DHP treatments, and the time lag between each PMX-DHP treatment, the combination therapies and the administration and setting of MV were highly varied.

In the present study, we found that PMX-DHP safely improved oxygenation and reduced the severity of SIRS in patients with rapidly progressive IP. Rapidly progressive IP, including AE-IP, can be lethal, and therapeutic criteria have not been established. Therefore, PMX-DHP has therapeutic potential for such patients. Further prospective controlled studies with large numbers of patients and a placebo group are required to address the limitations of the present study and to identify a suitable method for PMX-DHP administration to treat rapidly progressive IP.

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