SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2021; 38 (1); e2021012 DOI: 10.36141/svdld.v38i1.9734

Effectiveness of polymyxin B hemoperfusion in acute exacerbation of interstitial pneumonia: a retrospective analysis

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Abstract. Background; Acute exacerbation (AE) of interstitial pneumonia (IP) occurs commonly and has a poor prognosis. Polymyxin B hemoperfusion (PMX-DHP) has a beneficial effect on AE of some types of IPs, particularly idiopathic pulmonary fibrosis (IPF). However, little is known about the efficacy of PMX-DHP in the Korean population. The aim of this study was to examine the effectiveness of PMX-DHP in AE of IP. **Methods:** We conducted a retrospective study of 12 patients with AE of IP, including two patients with AE of IPF, who were treated with PMX-DHP at our center. Treatment with PMX-DHP was carried out once or twice. We collected and analyzed data on changes in oxygenation with PMX-DHP and survival after AE. **Results:** In patients with AE of IP, the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, or the P/F ratio, had significantly improved at the end of the treatment with PMX-DHP (87.0 [80.3 – 130.9] to 200.6 [105.0 – 245.5] mmHg, $p = 0.019$). The white blood cell (WBC) count had significantly reduced at the end of the treatment (12,400 [8,860 – 20,287] to 6,800 [3,950 – 15,775]/mm^3, $p = 0.050$). The 28-day and in-hospital mortality rates of patients after AE of IP were 41.7 % and 75.0 %, respectively. **Conclusion:** PMX-DHP improved oxygenation and reduced the WBC count in patients with AE, with either steroids alone or steroids and cyclophosphamide. Further studies are required to verify the potential benefits of PMX-DHP for patients with AE of IP.

Keywords: Lung Diseases; Interstitial; Disease Progression; Polymyxin B

Introduction

The clinical course of interstitial pneumonia (IP) is not clearly known and is highly variable (1-3). Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic IP (IIP). Acute exacerbation (AE) of IPF is now well defined. It pathologically shares tissue damage patterns of acute respiratory distress syndrome (ARDS), such as diffuse alveolar damage (DAD) (4). AE of IPF has a high mortality rate during hospitalization (5, 6). AE also occurs in non-specific IP, IP associated with connective tissue disease, and chronic hypersensitivity pneumonitis (7-10).

Direct hemoperfusion with polymyxin B-immobilized fiber column (PMX-DHP) is effective for sepsis (11) and ARDS (12, 13). PMX-DHP might favorably affect the endotoxin levels, ratio of partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2), or the P/F ratio, and mortality in patients with sepsis. PMX-DHP also has favorable effects on patients with acute lung injury (ALI) or ARDS with pathological DAD (12, 13).

Received: 7 May 2020
Accepted after revision: 5 February 2021

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Considering that the pathological findings of AE of IPF and ARDS are DAD, the use of PMX-DHP has been attempted in AE of IPF. In patients with AE of IPF, treatment with PMX-DHP significantly improves the P/F ratio and survival (14-17). Furthermore, in patients with other types of IPs, treatment with PMX-DHP improves the P/F ratio and survival (18-20). Since this has not been proven in the Korean population, the aim of this study was to investigate the safety and effectiveness of PMX-DHP in patients with IP.

Methods

Study population

We retrospectively examined the clinical records of consecutive patients with AE of IPF or other types of interstitial lung disease hospitalized and treated at the Chungnam National University Hospital from January 2018 to December 2019. AE of IPF was defined according to the criteria suggested by Collard et al (21). Patients who fulfilled the following criteria were diagnosed with AE of interstitial lung disease (ILD) (18, 19): (1) development or unexplained worsening of dyspnea within 30 days; (2) new bilateral ground-glass opacities and/or consolidation on high-resolution computed tomography; (3) stable P/F ratio < 300 mmHg; and (4) absence of apparent infection, pneumothorax, pulmonary thromboembolism, heart failure, and alternative causes of ALI, such as trauma, blood infusion, and toxic inhalation.

This study was approved by the Institutional Review Board of Chungnam National University (CNUH 2020-01-053), and the need for informed consent was waived because of the retrospective nature of the study.

PMX-DHP therapy

We administered PMX-DHP (PMX; Toray Medical Co., Ltd., Tokyo, Japan) to patients who were resistant to standard treatments, including corticosteroids alone or with cyclophosphamide. Treatment failure cases were defined as those where the oxygen demand did not decrease or increased after 24 hours after the clinician performed the standard treatment, and the PMX-DHP treatment was considered. A double-lumen catheter was inserted into the jugular or femoral vein. PMX-DHP was administered for 2 to 12 h (usually 6 h) at a flow rate of 100 mL/min and repeated once more within 24 h, if possible. Nafamostat mesilate was used as the anticoagulant.

Statistical analysis

Values are expressed as medians and interquartile ranges (IQRs) for continuous parameters. All statistical analyses were performed with the SPSS software, version 22.0 (IBM Corporation, Somers, NY, USA). We compared changes in the P/F ratio, vital signs, and other laboratory data between baseline and 24 or 48 h after the first PMX-DHP session using the Wilcoxon test. We performed comparisons between the two subgroups, IIP and non-IIP, using a general linear model for repeated measures. Cumulative survival was analyzed with the Kaplan–Meier method. Differences were considered significant at $p < 0.05$.

Results

Clinical features of patients

Table 1 shows the clinical characteristics of all patients. Twelve patients, including nine men and three women, with a median (IQR) age of 62.5 (56.0–77.5) years received a total of 20 cycles of PMX-DHP. Patients were classified into two subgroups: IIP (n = 7) and non-IIP (n = 5).

Most patients were diagnosed on the basis of radiologic findings, but one patient (No. 7) was diagnosed on the basis of findings of surgical biopsy. Two patients received corticosteroid therapy before onset, one of whom underwent immunosuppressive therapy with cyclophosphamide. One patient received pirfenidone before onset. Eight patients received mechanical ventilation with a median (IQR) duration of 12.0 (6.8–15.8) days.

Treatment and outcomes of patients

Table 2 shows the treatment and outcomes. Treatment with PMX-DHP was started after a median (IQR) duration of 48 (24.0 – 90.0) hours from the start of corticosteroid therapy. The median (IQR) number of cycles was two (one to two), and the median (IQR) duration was 6 (6 – 6) hours. Nine

Table 1. Clinical characteristics of patients

Patient Number	Sex	Age, years	Subgroup	Diagnosis	Duration of underlying disease, months	Previous therapy	Mechanical ventilation	Duration of ventilator
1	M	58	IIP	IPF	8	Pirfenidone	-	
2	M	66	IIP	IPF	0	-	+	9
3	M	71	IIP	Idiopathic AIP	0	-	-	
4	F	56	IIP	Idiopathic AIP	0	-	+	11
5	M	59	IIP	Unclassified IP	0	-	+	13
6	F	80	IIP	NSIP	0	-	-	
7	F	49	IIP	NSIP	0	-	+	16
8	M	56	Non-IIP	CPFE	18	-	+	15
9	M	84	Non-IIP	Drug-induced IP	0	-	+	6
10	M	78	Non-IIP	Drug-induced IP	0	-	-	
11	M	56	Non-IIP	DM-ILD	9	Steroid + Cyclophosphamide	+	4
12	M	76	Non-IIP	RA-ILD	15	Steroid	+	17

IIP: idiopathic interstitial pneumonia, IPF: idiopathic pulmonary fibrosis, AIP: acute interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, CPFE: combined pulmonary fibrosis and emphysema, IP: interstitial pneumonia, DM: dermatomyositis, ILD: interstitial lung disease, RA: rheymatoid arthritis

Table 2. Treatment and outcomes of patients

Patient Number	PMX-DHP				Treatment		Outcome	Survival (from 1st PMX-DHP day)	Hospital stay	ICU stay
	Starting from steroid pulse therapy, days	Cycles	Duration, hours	Time delay between each cycle, days	Steroid	Others				
1	3	2	6	1	1,000		Dead	39	42	4
2	2	2	2	1	500		Dead	52	60	10
3	17	2	6-12	1	1,000		Alive		22	3
4	5	1	6		1,000		Dead	11	19	11
5	2	1	6		60		Alive		368	30
6	2	2	6	1	500		Alive		21	6
7	4	2	6	1	1,000		Dead	15	30	16
8	1	2	6	1	500		Dead	52	52	25
9	1	2	6	1	60		Dead	29	30	30
10	1	1	6		1,000		Dead	3	5	3
11	1	1	6		500	Cyclopho-sphamide	Dead	3	7	4
12	1	2	6	1	500		Dead	13	24	19

PMX-DHP: polymyxin B-immobilized fiber column, ICU: intensive care unit

Table 3. Clinical course of laboratory data based on the Wilcoxon test

Value	Baseline		24 hours			48 hours		
	Median, IQR	n	Median, IQR	n	p-value	Median, IQR	n	p-value
Lab								
pH	7.43 (7.36 – 7.49)	12	7.4 (7.33 – 7.47)	12	0.875	7.4 (7.35 – 7.45)	12	0.724
PaCO2, mmHg	41.0 (37.3 – 51.3)	12	41.5 (38.0 – 55.5)	12	0.694	44.0 (36.5 – 53.8)	12	0.965
PaO2, mmHg	74.0 (62.3 – 83.0)	12	95.5 (81.8 – 134.8)	12	0.013	108.0 (58.8 – 121.5)	12	0.071
P/F ratio, mmHg	87.0 (80.3 – 130.9)	12	201.6 (116.3 – 242.5)	12	0.007	200.6 (105.0 – 245.5)	12	0.019
WBC, /uL	12,400 (8,860 – 20,287)	12	8,180 (5,960 – 11,032)	12	0.003	6,800 (3,950 – 15,775)	12	0.050
Hb, g/dL	11.1 (9.1 – 12.7)	12	10.4 (9.5 – 12.1)	12	0.119	10.6 (9.4 – 11.7)	12	0.307
Platelet, x10^3/uL	230.0 (83.3 – 285.5)	12	169.0 (68.0 – 212.3)	12	0.034	155.5 (52.0 – 206.0)	12	0.034
CRP, mg/dL	12.4 (3.1 – 24.7)	12	13.3 (2.1 – 14.7)	11	0.541	3.8 (1.9 – 11.9)	7	0.018
IL-6, pg/mL	46.8 (9.7 – 414.1)	12	38.6 (7.9 – 228.5)	12	0.347	43.9 (2.1 – 204.8)	9	0.594
Vital sign								
Mean BP, mmHg	88 (82 – 97)	12	86 (80 – 98)	12	0.844	86 (80 – 92)	12	0.694
Heart rate, beats/min	111 (86 – 119)	12	102 (81 – 116)	12	0.182	108 (90 – 124)	12	0.969
Respiratory rate, beats/min	23 (22 – 25)	12	24 (21 – 26)	12	0.330	23 (18 – 25)	12	0.201
Body temperature,°C	37.1 (36.7 – 37.4)	12	37.0 (36.6 – 37.3)	12	0.366	36.7 (36.4 – 36.9)	12	0.071

IQR: interquartile range, pH: potential hydrogen, PaCO2: partial pressure or carbon dioxide, PaO2: partial pressure of oxygen, P/F ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen, WBC: white blood cell, Hb: hemoglobin, CRP: C–reactive protein, IL-6: interleukin–6, BP: blood pressure

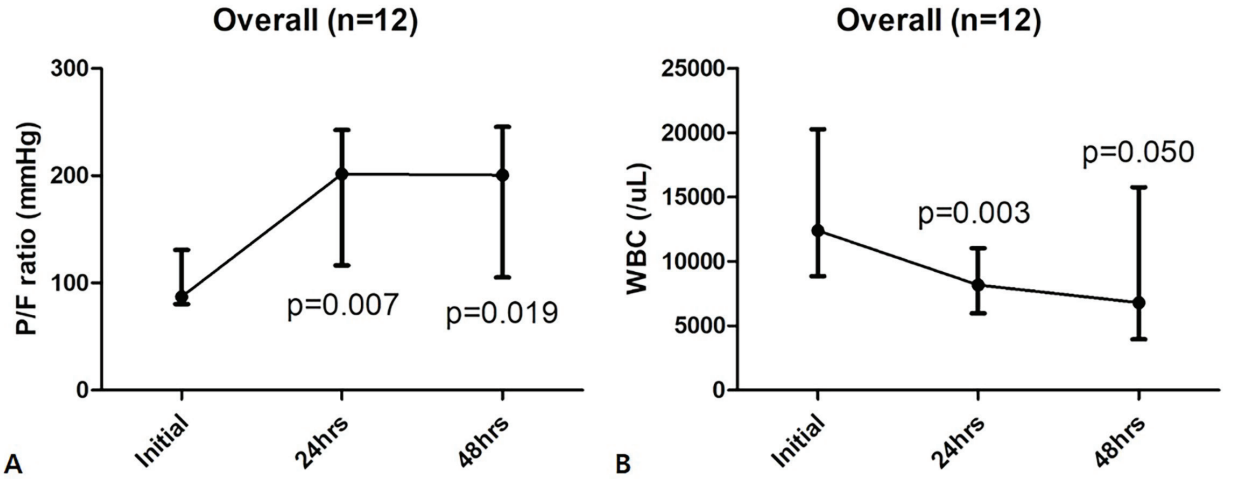

Figure 1. Change of P/F ratio and WBC count. The statistical analysis was performed with the Wilcoxon test. The p values indicate the comparisons with baseline values. Values are expressed as medians and IQRs (25 – 75%). A. P/F ratio, B. WBC
P/F ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen, WBC: white blood cell

Table 4. Change of laboratory data in subgroups

	Total	IIP (n = 7)	Non-IIP (n = 5)	p-value
Initial	12			
P/F ratio, mmHg	87.0 (80.3 – 130.9)	82.7 (76.3 – 191.7)	93.7 (82.0 – 125.4)	0.639
WBC, /uL	12,400 (8,860 – 20,287)	10,600 (6,840 – 14,400)	12,500 (12,210 – 23,275)	0.343
IL-6, pg/mL	46.8 (9.7 – 414.1)	14.0 (4.5 – 30.2)	277.4 (83.8 – 1748.5)	0.018
24 hours				
P/F ratio, mmHg	201.6 (116.3 – 242.5)	217.5 (197.1 – 250.0)	135.0 (82.0 – 233.9)	0.149
WBC, /uL	8,180 (5,960 – 11,032)	6,500 (4,700 – 11,110)	10,000 (8,180 – 15,950)	0.149
IL-6, pg/mL	38.6 (7.9 – 228.5)	13.0 (1.9 – 37.5)	288.0 (40.1 – 804.6)	0.010
48 hours				
P/F ratio, mmHg	200.6 (105.0 – 245.5)	197.8 (150.0 – 250.0)	203.3 (80.0 – 258.7)	0.755
WBC, /uL	6,800 (3,950 – 15,775)	5,180 (3,600 – 16,300)	8,900 (3,300 – 18,250)	0.530
IL-6, pg/mL	43.9 (2.1 – 204.8)	14.3 (1.9 – 66.0)	405.7 (324.9 – 405.7)	0.056

IIP: idiopathic interstitial pneumonia, P/F ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen, WBC: white blood cell, IL-6: interleukin-6

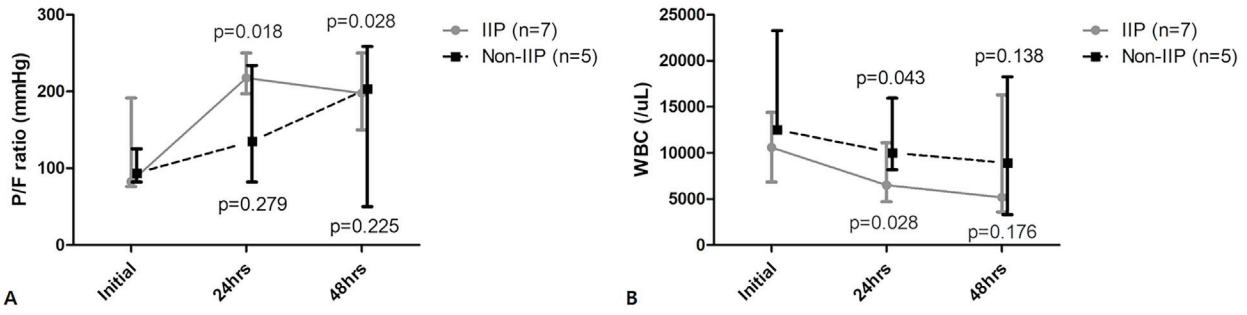

Figure 2. Change of P/F ratio and WBC count in the subgroup (IIP vs. non-IIP). The statistical analysis was performed with the Wilcoxon test. The p values indicate the comparisons with baseline values. Values are expressed as medians and IQRs (25 – 75%). A. P/F ratio, B. WBC
P/F ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen, WBC: white blood cell, IIP: idiopathic interstitial pneumonia

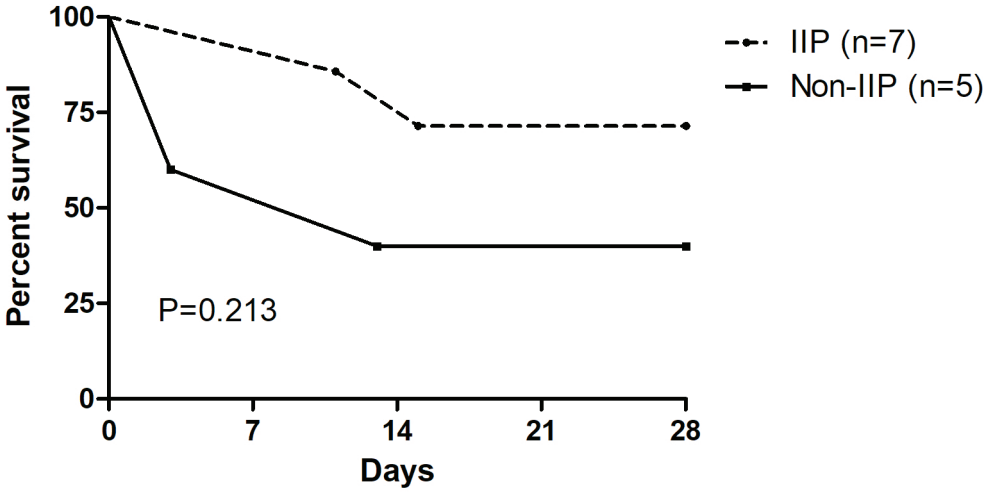

Figure 3. Comparison of the 28day-survival time of the patients in the subgroup. The median survival was longer and lower 28-day mortality in the IIP subgroup, but was not statistically significant by log-rank test (p = 0.213).
IIP: idiopathic interstitial pneumonia

of 12 patients died, and the median (IQR) survival after 1st PMX-DHP treatment among the patients who died was 15.0 (7.0 – 45.5) days. The median (IQR) duration of intensive care unit stay was 10.5 (4.0–23.5) days, and median (IQR) duration of hospital stay was 27.0 (19.5 – 49.5) days.

Clinical effects of PMX-DHP

The P/F ratio significantly improved in all patients from baseline to 24hours (median [IQR], 87.0 [80.3 – 130.9] mmHg vs. 201.6 [116.3 – 242.5] mmHg, p = 0.007) and 48hours (median [IQR], 87.0 [80.3 – 130.9] mmHg vs. 200.6 [105.0 – 245.5] mmHg, p = 0.019) after the 1st PMX-DHP treatment (Table 3, Figure 1A). Moreover, improvement in the P/F ratio after 24hours (p = 0.018) and 48hours (p = 0.028) was statistically significant in the IIP subgroup but not in the non-IIP group (24hours: p = 0.279; 48hours: p = 0.225) (Figure 2A). However, there was no statistically difference between the two subgroups (Table 4).

The WBC count significantly decreased in all patients from baseline to 24hours (median [IQR], 12,400 [8,860 – 20,287] vs. 8,180 [5,960 –11,032], p = 0.003) and 48hours (median [IQR], 12,400 [8,860

– 20,287) vs. 6,800 [3,950 – 15,775], p = 0.050) after the 1st PMX-DHP treatment (Table 3, Figure 1B). Moreover, decrement in the WBC count after 24 hours in both subgroups was statistically different (IIP: p = 0.028; non-IIP: p = 0.043) but not after 48 hours (IIP: p = 0.176; non-IIP: p = 0.138) (Figure 2B). However, there was no statistically difference between the two subgroups (Table 4).

The 28-day mortality was 41.7 % (five of 12 patients), and in-hospital mortality was 75.0 % (nine of 12 patients). The median (IQR) survival was 27.0 (19.5 – 49.5) days from admission and 15.0 (7.0 – 45.5) days from the 1st PMX-DHP treatment. In subgroup comparisons performed with the log-rank test, the 28-day and in-hospital mortalities were 28.6 % (two of seven patients) and 57.1 % (four of seven patients), respectively, in the IIP subgroup and 60.0 % (three of five patients) and 100.0 % (five of five patients), respectively, in the non-IIP subgroup (p = 0.213, p = 0.085) (Figure 3).

Side effects of PMX-DHP

To clarify the safety of PMX-DHP, we investigated the clinical course of vital signs and laboratory data (Table 3). Vital signs did not deteriorate during the PMX-DHP treatment, and no patient required additive vasopressors. None of the patients showed a tendency to bleed or required blood transfusion during the PMX-DHP treatment. There were no complications, such as pneumothorax or hematoma, associated with catheter insertion.

Discussion

This is the first study in Korea to retrospectively investigate the PMX-DHP treatment of patients with AE of IP. We found that PMX-DHP improved oxygenation and reduced the WBC count. Improved oxygenation and reduction in WBCs were found in both IIP and non-IIP subgroups. No improvement in survival was clearly identified. There were no complications during the PMX-DHP treatment.

Polymyxin B effectively reduces the level of endotoxins in blood during sepsis. The addition of PMX-DHP to conventional therapies improved survival of patients with sepsis and/or septic shock caused by abdominal gram-negative infections (11). The most common cause of ARDS is sepsis, a serious and widespread infection of the bloodstream. PMX-DHP improved the circulatory instability, oxygenation, and survival in patients with ARDS (12, 13). ARDS may be pathologically characterized by diffuse inflammatory findings in lung parenchyma, such as DAD, which is the most common surgical biopsy finding in AE with usual interstitial pneumonia (UIP) (4). Seo et al. first investigated the effect of the PMX-DHP treatment on AE of IPF. With the conventional corticosteroid treatment, four of six patients could be successfully weaned from mechanical ventilation and survived for over 30 days after the initial PMX treatment (14).

In this study, the P/F ratio improved in patients who received PMX-DHP, consistent with previous studies. Abe et al. reported that in patients with AE of IPF, the P/F ratio had significantly improved at the end of the 2nd treatment with PMX (mean ± standard error of mean [SEM] 173.9 ± 105.4 to 195.2 ± 106.8 Torr, p = 0.003) (15). Enomoto et al. reported that in patients with IPF, treatment with PMX-DHP elicited a significantly greater change in the P/F ratio (mean ± SEM, 58.2 ± 22.5 vs. 0.7 ± 13.3, p = 0.034) after 2 days compared to patients treated without PMX-DHP (17). Hara et al. reported that in patients with rapidly progressive IPs, the P/F ratio significantly improved 72 hours after PMX-DHP (median [IQR], 127.0 [91.1–150.9] vs. 152.8 [116.5–274.4], p = 0.02) (18). The mechanism through which PMX-DHP improves oxygenation in patients with AE of IP is unclear. However, Hara et al. found that the serum level of monocyte chemoattractant protein-1 (MCP-1) after PMX-DHP treatment had significantly reduced compared to the level before the PMX-DHP treatment (18). MCP-1 is produced by various cells, including monocytes. It belongs to the CC subgroup of chemokines and plays an important role in the recruitment and activation of monocytes during acute inflammation (22). MCP-1 is elevated in the bronchoalveolar lavage fluid and serum of patients with IPF or other types of IP (23, 24). Similarly, elevated CXC chemokines are associated with the pathological condition of IPF and other types of IP (25-27). Some inflammatory chemokines (e.g., neutrophil elastase, interleukin-8 (28), and interleukin-18 (29)) are immediately reduced in patients with ARDS after PMX-DHP. Seo et al. showed that reduction in interleukin-6 and interleukin-8 and plasminogen activator inhibitor-1 was found after

PMX-DHP (14). Noma et al. reported that MCP-1, interleukin-6, and interleukin-8 had reduced 72 h after PMX-DHP (30). These studies suggested that oxygenation improves because of the reduction in chemokines after PMX-DHP, but further studies are required.

In this study, the WBC count had decreased after the PMX-DHP treatment. Abe et al. showed that the WBC count had significantly reduced at the end of the 2nd treatment (13,330 ± 7,002 to 9,426 ± 5,188/mm^3, $p < 0.001$) (15). Enomoto et al. showed a smaller change in the WBC count (–630 ± 959 / μL vs. 4,500 ± 1190 /μL, $p = 0.002$) after 2 days of treatment (17). Enomoto et al. reported that three of the four patients with AE of IP who received 6- or 12-hours courses of PMX-DHP showed a decrease in serum interleukin-6 levels after PMX-DHP (20). Abe et al. showed PMX-DHP treatment in patients with acute exacerbation of interstitial pneumonia. After treatment, the cells absorbed by PMX were neutrophils and highly expressed HLA-DR, CD14, CD62L, and CD114. Additionally, serum MMP-9, which plays an important role in acute exacerbation of IP or acute respiratory distress syndrome, decreased after PMX (31). These studies showed reductions in WBC and chemokines, which may help improve the AE status through the reduction of inflammatory effects.

In this study, improvement in mortality was not confirmed in patients undergoing PMX-DHP, but there was a potential for improvement. Seo et al. reported that patients with AE of IPF survived more than 30 days after the PMX treatment (14). Takada et al. reported that six patients with rapidly progressive ILD who underwent PMX-DHP on the 1st day of steroid pulse therapy had significantly longer survival times than those who were treated with standard medication alone ($p < 0.01$) (19). Enomoto et al. reported that among patients with AE of IPF, the 12-month survival rate was significantly higher in patients treated with PMX-DHP (48.2 % vs. 5.9 %, $p = 0.041$). Treatment with PMX-DHP was an independent predictor of better prognosis (hazards ratio: 0.345; $p = 0.037$) (17). In our study, 28-day and in-hospital mortalities were 41.7 % and 75.0 %, respectively. AL-Hameed et al. described outcomes of AE of IPF in patients who were admitted to the intensive care unit. In their study, 24 of 25 patients died, resulting in overall mortality of 96% (6). Comparing these results, treatment with PMX-DHP might help improve survival.

Limitations

This study has some limitations. First, it was a small, retrospective, observational study at a single center. The pathological findings were unclear in most patients. In addition, the etiology, underlying disease and treatment, frequency and duration of the PMX-DHP treatment, time delay between every two PMX-DHP treatments, combination therapy, and adjustment of mechanical ventilation were diverse.

Conclusion

In conclusion, oxygenation improved stably without complications and the WBC count decreased when PMX-DHP was performed in patients with AE of IP. Improvements in survival were not statistically significant but may be of benefit for further studies. For patients with AE of IP, no particularly effective treatment could be established, and the prognosis was poor. Therefore, a large prospective trial is warranted for the future to confirm the improvement of the clinical course and survival of patients with AE of IP following the use of PMX-DHP.

Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

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