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ORIGINAL RESEARCH

Estimation of treatment and prognostic factors of pneumocystis pneumonia in patients with connective tissue diseases

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ABSTRACT

Objectives To investigate short-term prognosis and prognostic factors for connective tissue disease-associated pneumocystis pneumonia (CTD-PCP) using the Japanese nationwide diagnosis procedure combination (DPC) inpatient database.

Methods The present retrospective cohort study from April 2014 to March 2016 included data of patients with CTD-PCP extracted from the DPC database using the 10th revision of International Classification of Diseases and Injuries codes.

Results In 15 901 766 cases registered from 1329 hospitals, 333 of 67 890 patients who were admitted with PCP were diagnosed with CTD-PCP and included in the study. The median age was 71.0 years, and 214 (64.3%), 80 (24.0%), and 29 (8.7%) patients received sulfamethoxazole/trimethoprim (ST) monotherapy and pentamidine-containing and atovaquone-containing therapy, respectively. There were 114 (34.2%) in-hospital deaths, and the 30-day and 60-day in-hospital survival rates after PCP treatment initiation were 66.0% and 53.7%, respectively. Older age (HR 1.06, 95% CI 1.03 to 1.08) and concomitant interstitial lung disease (ILD) (HR 1.65, 95% CI 1.12 to 2.42) were poor prognostic factors. Patients who completed PCP treatment with ST monotherapy had a significantly higher survival rate than those treated with those not treated with ST monotherapy (p=0.015; log-rank test). Pentamidine versus atovaquone as second-line therapy was significantly higher with atovaquone (p=0.012; log-rank test).

Conclusion Older age and concomitant ILD were poor prognostic factors for CTD-PCP. ST was a reasonable first-line therapy in patients with CTD-PCP, and patients with inadequate response to ST treated with atovaquone tended to have a better prognosis than those treated with pentamidine.

Key messages

What is already known about this subject?

- Pneumocystis pneumonia (PCP), an opportunistic infection commonly associated with HIV, is also observed in patients with connective tissue diseases (CTD) undergoing immunosuppressive therapy. The reported mortality rate of CTD-associated PCP (CTD-PCP) is higher than that of HIV-associated PCP (HIV-PCP).

What does this study add?

- Previous reports on CTD-PCP are limited to single-centre observational studies and those including CTD-PCP as part of a larger cohort of non-HIV-PCP cases. The clinical course and prognostic factors of CTD-PCP remain unclear due to the lack of large studies focusing on CTD-PCP. We therefore used the diagnosis procedure combination database, a national administrative inpatients database in Japan, to address this gap in knowledge.

How might this impact on clinical practice?

- Using a large Japanese national database, this is the first study to show that CTD-PCP is a fatal complication with a mortality rate of more than 30% and that older age and concomitant interstitial lung disease are poor prognostic factors. Our analyses also reveal that sulfamethoxazole/trimethoprim is a reasonable first-line treatment option and that atovaquone might be considered as an appropriate second-line treatment option.

INTRODUCTION

Pneumocystis pneumonia (PCP) is a fatal complication that occurs in immunocompromised individuals, such as patients infected with HIV and those with connective tissue diseases (CTDs) receiving immunosuppressive therapy with glucocorticoids (GCs) and/or immunosuppressants. The reported mortality rate of CTD-associated PCP (CTD-PCP) is higher than that of HIV-associated PCP (HIV-PCP). However, no large clinical studies to date have focused on CTD-PCP, and published reports on the clinical course and prognosis of CTD-PCP have been limited to observational studies in a small number of centres and to those including CTD-PCP as part of a larger cohort of non-HIV-PCP cases, including our previous reports, because of the number of cases of CTD-PCP is smaller than that of HIV-PCP.[1–5] High doses of

sulfamethoxazole/trimethoprim (ST; trimethoprim dose, 15–20 mg/kg/day) generally comprise the first-line therapy for patients with moderate/severe PCP.[6–8] However, the ST doses for PCP treatment are relatively high and often require reduction or discontinuation due to adverse effects. In patients with inadequate response to ST, second-line therapies such as atovaquone and pentamidine may be used.[9] No randomised controlled trials have evaluated antibiotics in patients with CTD-PCP, and few studies have directly compared the efficacy and safety of specific antibiotics or outcomes of second-line therapeutic options such as those used in patients switching from ST. Therefore, we performed an observational study using a large, real-world database in Japan, a country with a relatively high incidence of CTD-PCP, to investigate the prognosis and prognostic factors in patients treated with specific antibiotics for CTD-PCP.

METHODS

Study design and participants

This was a retrospective cohort study using the diagnosis procedure combination (DPC) database of inpatients in Japan, which comprises all advanced treatment hospitals including all university hospitals and many acute-care community hospitals.[10] Patient information recorded into the DPC database includes age, sex, diagnosis based on the 10th revision of International Classification of Diseases and Injuries (ICD-10) codes at the time of admission, comorbidities, complications after admission and information related to treatment and procedures (eg, drug names, procedures and costs). The DPC database also contains information on the amount and duration of administered drugs, blood products used, length of hospital stay and outcomes at discharge.[11 12] All data were reentered into the DPC database by a physician or professionally trained medical staff who handled the medical information. The data included in this article were provided by The DPC Study Group by permission. Data will be shared on reasonable request to the corresponding author with permission from The DPC Study Group.

Informed consent was waived for all patients included in the present retrospective cohort study, and all information extracted from the enrolled patients was anonymised.

First, 67 890 patients admitted with PCP were extracted from the DPC database among 15 901 766 inpatient cases from 1329 hospitals registered in the DPC database between 1 April 2014 and 31 March 2016. Second, patients with CTD-PCP were defined as those who had a CTD diagnosis and were administered specific antibiotics (ST, atovaquone or pentamidine) for more than seven consecutive days to treat PCP. After the exclusion of 67 890 patients with PCP in the absence of a CTD diagnosis, there were a total of 333 patients with CTD-PCP, who were included in the study (figure 1).

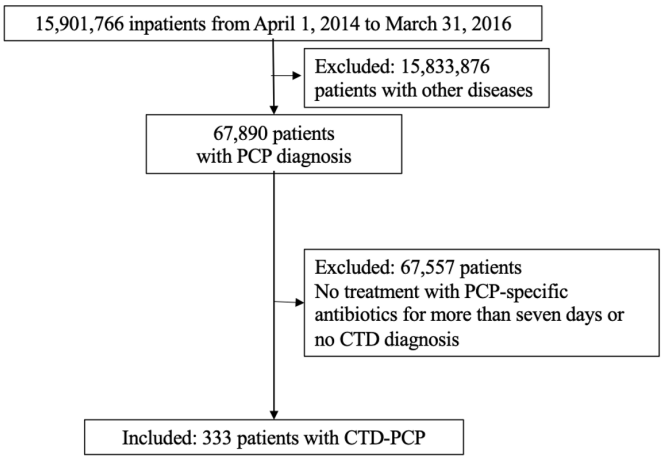

Figure 1 Flow chart of the study and analysis. CTD, connective tissue disease; PCP, pneumocystis pneumonia.

Definition of CTD-PCP

The principal diagnosis of CTD was recorded using the following ICD-10 codes: M329 (adult-onset Still's disease), M352 (Behçet's disease), M341 (CREST syndrome), M308 (cutaneous polyarteritis nodosa), M329 (dermatomyositis), M354 (eosinophilic fasciitis), M301 (eosinophilic granulomatosis with polyangiitis), M500 (Felty syndrome), M316 (giant-cell arteritis), M313 (granulomatosis with polyangiitis), M359 (IgG4-related disease), M510 (Kaplan syndrome), M321 (lupus nephritis), M530 (malignant rheumatoid arthritis (RA)), M300 (microscopic polyangiitis), M351 (mixed CTD/overlap syndrome), M300 (polyarteritis nodosa), M352 (polymyalgia rheumatica (PMR)), M332 (polymyositis), M600 (remitting seronegative symmetrical synovitis with pitting oedema), M339 (respiratory disorders due to dermatomyositis), M348 (respiratory disorders due to systemic sclerosis), M600 (RA), M510 (rheumatoid interstitial lung disease (ILD)), M520 (rheumatoid vasculitis), M349 (scleroderma), M610 (seronegative RA), M350 (Sjögren's syndrome), M329 (systemic lupus erythematosus), M340 (systemic sclerosis) and M314 (Takayasu arthritis). The principal diagnosis of PCP was based on the ICD-10 code J173.

It was expected that using the ICD-10 codes alone would identify patients who were not actually treated for PCP as well as those with suspicious PCP who initiated PCP treatment but switched to another therapeutic approach after a change in diagnosis. Therefore, based on a previous report assessing initial response to PCP treatment 7 days after the start of treatment, the present study defined patients with CTD-PCP as those with a CTD diagnosis who received one or more of the following PCP-specific antibiotics for more than seven consecutive days[13]: ST (at least four tablets daily), pentamidine and atovaquone (750 mg two times per day). ST is generally administered at a lower dose in patients with renal dysfunction. Per the Japanese pharmaceutical reference, ST is recommended at half the usual dosage (9–12 tablets daily) in patients with renal dysfunction. Therefore, four

tablets daily were set as the lower dose limit for PCP treatment because doses below four tablets could have been administered for prophylaxis.

Study outcomes

The primary outcome was overall in-hospital survival at 30 and 60 days after initiation of treatment for CTD-PCP. The study also aimed to investigate prognostic factors associated with in-hospital mortality with CTD-PCP and PCP-specific antibiotic treatment.

Statistical analysis

Categorical variables were presented as numbers (%), and continuous variables were presented as medians with IQR or numbers with percentages (%). An independent samples t-test was used to evaluate normally distributed data, and the Mann-Whitney test was employed to evaluate non-normally distributed data for comparison between two groups. Classification data number (percentage) aggregation, and the χ^2 or Fisher's exact test. The Kaplan-Meier plots and log-rank test were used to compare survival rates among groups. Associations among covariates and risk of mortality requiring dialysis were evaluated using the Cox proportional hazards regression analysis, and HRs with 95% CIs were determined after adjusting for potential confounders. Confounding factors reported in previous studies (age, sex, and concomitant ILD) were preferentially selected as explanatory variables for multivariate analysis using the Cox proportional hazards regression. The type of CTD (RA and PMR, primary vasculitis syndrome, systemic lupus erythematosus, inflammatory myositis and systemic sclerosis) was also included in the analysis model as an explanatory variable because mortality due to PCP has been suggested to differ among different CTDs in previous studies.[14–18] All tests were two-tailed, and a $p<0.05$ was considered to indicate statistical significance. All statistical analyses were performed using the R software package (V.4.0.0, R Foundation).[19]

RESULTS

Patient characteristics

Among the 15 901 766 inpatients registered from 1329 hospitals between 1 April 2014 and 31 March 2016, 67 890 admitted for PCP were extracted from the DPC database. Among these, 333 patients with CTD were registered as CTD-PCP for final analysis.

The baseline characteristics of the study cohort are shown in table 1. The median age (IQR) was 71.0 (62.0, 77.0) years, and 210 patients (63.1%) were women. The cohort comprised 104 (31.2%), 109 (32.7%) and 120 (36.0%) patients who were <65 years, 65–74 years (preold age) and ≥75 years (old age) of age, categorised based on the Japanese Gerontological Society and the Japan Geriatrics Society.[20] Additionally, 122 patients (36.6%) had concomitant ILD. The cohort comprised 52 (15.6%) and 281 (84.1%) patients in the RA (including RA and/or PMR) and non-RA groups, respectively. The most common CTDs in the non-RA group were primary vasculitis (n=116, 34.8%), inflammatory myositis (n=60, 18.0%) and systemic lupus erythematosus (n=49, 14.7%). Furthermore, 37 patients (11.1%) required intensive care management and 83 patients (24.9%) required ventilator support. GCs were administered in almost all patients (n=322, 96.7%), and GC pulse therapy was given in 103 patients (30.9%). Regarding specific antibiotics for PCP treatment, 214 patients (64.3%) were treated with ST monotherapy.

Study outcomes: survival rates and prognostic factors

There were 114 in-hospital deaths (34.2 %) in the study cohort. The baseline characteristics of the survivor and non-survivor groups are summarised in table 2. Compared with the survivors, the non-survivors were significantly older and had significantly higher rates of vasculitis and concomitant ILD. Comparison of the treatment approaches between the two groups revealed that there were more patients receiving intensive care management and ventilator support, GC pulse therapy, pentamidine-including second-line therapy (ie, pentamidine-including group comprising patients treated with pentamidine monotherapy and those who switched from ST to pentamidine), immunoglobulin, albumin preparation, general antibiotics, antifungal drugs and anticytomegalovirus drugs in the non-survivor group than in the survivor group. Conversely, the rate of ST monotherapy was significantly higher in the survivor group.

The Kaplan-Meier survival curves of CTD-PCP are shown in figure 2A. The estimated survival rates at 30 and 60 days after the start of treatment for CTD-PCP were 66.0% and 53.7%, respectively. We next analysed poor prognostic factors associated with in-hospital mortality due to CTD-PCP using the Cox proportional hazards regression model (table 3). Using the multivariable analysis, older age (HR 1.05, 95% CI 1.03 to 1.08, $p<0.001$) and concomitant ILD (HR 1.65, 95% CI 1.12 to 2.42, $p=0.012$) were poor prognostic background factors. Vasculitis, which was a significant factor in the univariable analysis, was not a poor prognostic factor in the multivariable analysis. Most patients with vasculitis were older (mean age, 74.3 vs 68.2 years in the overall cohort; $p<0.001$), suggesting that age might be a major confounding factor. The Kaplan-Meier survival curves by the three age groups are shown in figure 2B. Briefly, the 30-day and 60-day survival rates significantly declined with increasing age (82.4% and 76.3%, 65.8% and 50.1%, and 53.3% and 39.9%, respectively, in the <65 year, 65–74 year, and ≥75 year age groups, respectively). With the <65 year age group as reference, the HRs were 2.77 (95% CI 1.60 to 4.90) and 3.56 (95% CI 2.03 to 6.25) for the 65–74 year and ≥75 year age groups, respectively ($p<0.001$, log-rank test). The Kaplan-Meier survival curves in patients categorised according to the presence of concomitant ILD are shown in figure 2C. The 30-day and 60-day survival rates

Table 1 Patient characteristics

	N	%	Median (IQR)
Patients	333		
Death	114		
Age, years			71 (62–77)
<65	104	31.2	
65–74	109	32.7	
≥75	120	36.0	
Female	210	63.1	
RA and PMR	52	15.6	
Psoriatic arthritis and spondylarthritis	0	0.0	
Primary vasculitis syndrome	116	34.8	
Systemic lupus erythematosus	49	14.7	
Inflammatory myositis	60	18.0	
Systemic sclerosis	13	3.9	
Others	43	12.9	
Concomitant ILD	122	36.6	
Admission to an advanced treatment hospital	94	28.2	
Bronchoscopy	36	10.8	
Intensive care management	37	11.1	
Ventilator use	83	24.9	
Length of hospital stay after starting PCP treatment, days			33 (4–37)
Glucocorticoid therapy			
Concomitant glucocorticoid use	322	96.7	
Glucocorticoid pulse therapy	103	30.9	
Antibiotics for PCP			
ST monotherapy	214	64.3	
Others	119	35.7	
PTM group	80	24.0	
PTM monotherapy	32	8.4	
ST → PTM	48	14.4	
ATO group	29	8.7	
ATO monotherapy	9	2.7	
ST → ATO	20	6.0	
Other combinations	10	3.0	
Adjunctive therapy			
Gamma-globulin	31	9.3	
Albumin	40	12.0	
Empiric antibiotic therapy	245	73.6	
Antifungal drugs	110	33.0	
Anticytomegalovirus drugs	56	16.8	

ATO, atovaquone; ILD, interstitial lung disease; PCP, pneumocystis pneumonia; PMR, polymyalgia rheumatica; PTM, pentamidine; RA, rheumatoid arthritis; ST, sulfamethoxazole/trimethoprim.

were significantly lower in patients with concomitant ILD (58.3% and 47.5%, respectively) than in those without concomitant ILD (71.6% and 57.5%, respectively; HR 1.60, 95% CI 1.11 to 2.32; p=0.011, log-rank test).

Treatment for CTD-PCP

ST is generally used as the first-line antibiotic for PCP. Therefore, we primarily compared survival rates between the patients who were treated with ST monotherapy and those who were treated with antibiotics other than ST or a combination of ST and other antibiotics (others group) to evaluate the efficacy of first-line treatment with ST for CTD-PCP. There were no significant differences in patient background characteristics between the ST monotherapy and others groups (table 4). The comparison of survival

Table 2 Comparison of the clinical features between the survivors and non-survivors

	Survivors		Non-survivors		
	N=219	%	N=114	%	P value
Age, years (median, IQR)	65.3 (57–76)		73.6 (68–81)		<0.001
Female	146	66.7	64	56.1	0.073
RA and PMR	37	16.9	15	13.2	0.428
Non-RA and PMR	182	83.1	99	86.8	
Primary vasculitis syndrome	63	28.8	53	46.5	0.002
Systemic lupus erythematosus	32	14.6	17	14.9	1.000
Inflammatory myositis	45	20.5	15	13.2	0.101
Systemic sclerosis	10	4.7	3	2.6	0.554
Others	32	14.6	11	9.6	0.231
Concomitant ILD	70	32.0	52	45.6	0.017
Admission to an advanced treatment hospital	66	30.1	28	24.6	0.284
Bronchoscopy	25	11.4	11	9.6	0.712
Intensive care management	12	5.5	25	21.9	<0.001
Ventilator use	16	7.3	67	58.8	<0.001
Length of hospital stay after starting PCP treatment	35.8 (6–24)		27.3 (4–18)		0.034
Concomitant glucocorticoid use	210	95.9	112	98.2	0.343
Glucocorticoid pulse therapy	46	21.0	57	50.0	<0.001
ST monotherapy	154	70.3	60	52.6	0.017
Others	65	29.7	54	47.4	
PTM monotherapy or ST → PTM (PTM group)	34	15.5	46	40.4	<0.001
ATO monotherapy or ST → ATO (ATO group)	24	10.9	5	4.4	0.063
Other combinations	7	3.3	3	2.6	1.000

t-test, the Mann-Whitney test, χ^2 test and Fisher's exact test were used when appropriate to compare the groups.
ATO, atovaquone; ILD, interstitial lung disease; PCP, pneumocystis pneumonia; PMR, polymyalgia rheumatica; PTM, pentamidine; RA, rheumatoid arthritis; ST, sulfamethoxazole/trimethoprim.

rates between the ST monotherapy and other groups is shown in figure 2D. Briefly, both the 30-day and 60-day survival rates were significantly higher in the ST monotherapy group than in the others group (30-day and 60-day survival rates, ST monotherapy group, 79.0% and 76.6% versus others group, 63.0% and 58.5%, respectively; HR 0.64, 95% CI 0.44 to 0.82, p=0.015, log-rank test). Pentamidine or atovaquone was generally used in patients with inadequate response to ST.

The patients who were treated with pentamidine (n=32) and those who were switched from ST to pentamidine (n=48) were categorised as the pentamidine group (n=80), whereas the patients who were treated with atovaquone (n=9) monotherapy and those who were switched from ST to atovaquone (n=20) were categorised as the atovaquone group (n=29). Although there were no significant differences in patient background characteristics between pentamidine and atovaquone groups (table 4), both the 30-day and 60-day survival rates were significantly higher in the atovaquone group than in the pentamidine group (30-day and 60-day survival rates, atovaquone group, 82.2% and 82.2% vs pentamidine group, 49.0% and 37.7%, respectively; HR 3.06, 95% CI 1.22 to 7.73, p=0.018, log-rank test) (figure 2E).

DISCUSSION

The present observational study including 333 patients with CTD-PCP using the DPC database, a Japanese nationwide database, revealed that CTD-PCP remained a fatal complication and that older age and concomitant ILD were background factors associated with poor prognostic. Among patients with inadequate response to ST, the prognosis was better in those who received atovaquone compared with pentamidine as second-line treatment. The results of the present nationwide study with a larger cohort of patients provide stronger support to previous reports showing older age and concomitant ILD as risk and poor prognostic factors for PCP.[14–18]

Because of the relatively good prognosis of patients treated with ST alone, ST might be considered as a reasonable first-line antibiotic for CTD-PCP as well as for HIV-PCP. However, patients treated with ST monotherapy might have been less likely to have complications such as chronic kidney disease, which is a prognostic factor

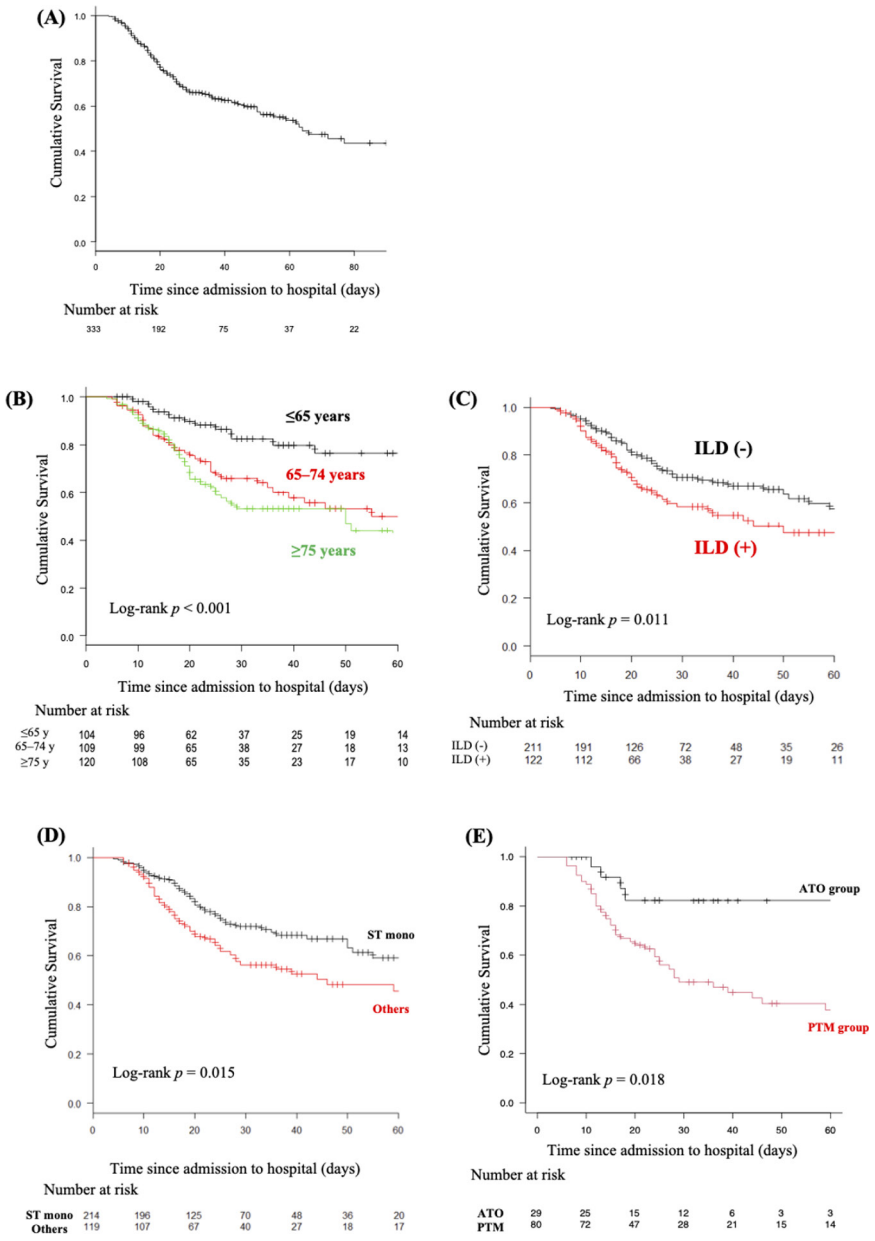

Figure 2 (A) Estimated Kaplan-Meier overall survival curve of patients with connective tissue disease-associated pneumocystis pneumonia (CTD-PCP). (B) Estimated Kaplan-Meier overall survival curves of patients with CTD-PCP by age category. (C) Estimated Kaplan-Meier overall survival curves of patients with CTD-PCP with or without interstitial lung disease (ILD). (D) Estimated Kaplan-Meier overall survival curves of patients with CTD-PCP who completed sulfamethoxazole/trimethoprim (ST) monotherapy (mono). (E) Estimated Kaplan-Meier overall survival curves of patients with CTD-PCP who were treated with second-line therapy (pentamidine (PTM) or atovaquone (ATO)).

for PCP and should be considered as a confounding factor.[21] The present study results suggest that the prognosis might be relatively poor in patients treated with pentamidine-including regimens. Since low-dose ST with 4–10 mg/kg/day trimethoprim has also been suggested to be as effective as high-dose ST in patients with non-HIV-PCP, a reduction in ST dose might be considered as a next step in patients with inadequate response to ST.[22] There are several potential reasons that might explain the poor prognosis observed in the pentamidine group. Pentamidine is administered intravenously and might have been used in patients with relatively poor general condition. In addition, pentamidine has a relatively high rate of side adverse effects such as renal dysfunction, cytopenia and abnormal glucose tolerance and it cannot be denied that patients treated with pentamidine might not have been treated with a sufficient dose for an adequate length of time. Studies suggest that pentamidine as first-line or second-line treatment is associated with high risk of death and may require a change in treatment in patients with HIV-PCP.[23] Therefore, pentamidine should be used in carefully selected individuals, such as those with severe disease exhibiting inadequate response to ST and/or atovaquone.

Table 3 Prognostic factors for survival

		Univariable Cox hazard analysis			Multivariable Cox hazard analysis		
Variable	**N**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age		1.05	1.03 to 1.07	<0.001	1.06	1.03 to 1.08	<0.001
Male	128	Ref			Ref		
Female	205	0.62	0.43 to 0.90	0.012	0.75	0.51 to 1.11	0.158
Concomitant ILD	122	1.60	1.11 to 2.32	0.012	1.65	1.12 to 2.42	0.012
RA and PMR	52	0.97	0.56 to 1.67	0.901	0.98	0.44 to 2.20	0.967
Primary vasculitis syndrome	116	1.63	1.12 to 2.36	0.010	1.14	0.57 to 2.26	0.711
Systemic lupus erythematosus	49	0.87	0.51 to 1.46	0.589	2.07	0.94 to 4.58	0.071
Inflammatory myositis	60	0.69	0.40 to 1.18	0.177	1.15	0.52 to 2.54	0.722
Systemic sclerosis	13	0.71	0.22 to 2.23	0.552	0.81	0.22 to 2.96	0.746
Others	43	0.82	0.21 to 3.23	0.775			
Oxygen administration on admission	76	0.84	0.52 to 1.35	0.465			

Univariable and multivariable Cox proportional hazards regression analyses were performed.
ILD, interstitial lung disease; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; Ref, reference.

Atovaquone has been reported to be a relatively well-tolerated antibiotic for PCP.[24 25] In the present study, the 30-day and 60-day survival rates were comparable between the ST monotherapy (79.0% and 76.6%, respectively) and atovaquone (72.2% and 72.2%, respectively) groups. It is possible that, as an oral antibiotic, atovaquone might have been administered to patients in relatively good general condition in the current study. On the basis of the results, the efficacy of atovaquone may be comparable with that of ST for mild to moderate CTD-PCP cases that can be treated orally. Future studies with a larger number of cases are warranted for the assessment of patient background characteristics such as severity of pneumonia and renal dysfunction to further elucidate the role of atovaquone in outcomes of patients with CTD-PCP. This study was conducted using the DPC data encompassing a 2-year period starting in April 2014. The limited number of patients treated with atovaquone was due to its recent approval for use in Japan in 2012; atovaquone might not have been widely used for the treatment of PCP during the observation period. Nonetheless, the present study findings show for the first time that ST was a reasonable first-line treatment for CTD-PCP and that the prognosis with atovaquone was better than that with pentamidine in patients receiving second-line antibiotic treatment following inadequate response to ST. 'Consensus statements for medical practice: Biological agents and lung diseases,' which includes a description of PCP, was published in 2014 in Japan.[26] Although PCP has been described in patients using biologics, information

Table 4 Comparison of the clinical features by treatment group

	ST monotherapy		Other			PTM		ATO		
	N=214	**%**	**N=119**	**%**	**P value**	**N=80**	**%**	**N=29**	**%**	**P value**
Age (median, IQR)	71.0 (60.0–77.0)		71.0 (63.0–77.5)		0.640	71 (65–76)		73 (59–81)		0.942
Female	135	63.1	75	63.0	1.000	48	60.0	19	65.5	0.661
RA and PMR	30	14.0	22	18.5	0.345	13	16.3	7	24.1	0.403
Non-RA and PMR	184	86.0	97	81.5		67	83.8	22	75.9	
Primary vasculitis syndrome	82	38.3	34	28.6	0.093	25	31.3	8	27.6	0.816
Systemic lupus erythematosus	26	12.1	23	19.3	0.106	17	21.3	3	10.3	0.267
Inflammatory myositis	36	16.8	24	20.2	0.460	14	17.5	7	24.1	0.425
Systemic sclerosis	9	4.2	4	3.4	0.777	1	1.3	2	6.9	0.172
Others	31	14.5	12	10.1	0.307	10	12.5	2	6.9	0.510
Concomitant ILD	84	39.3	38	31.9	0.194	26	32.5	7	24.1	0.484
Oxygen administration on admission	49	22.9	27	22.7	1.000	14	17.5	10	34.5	0.071

t-test, the Mann-Whitney test, χ^2 test and Fisher's exact test were used when appropriate to compare the groups.
ATO, atovaquone; ILD, interstitial lung disease; PMR, polymyalgia rheumatica; PTM, pentamidine; RA, rheumatoid arthritis.

is limited on treatment recommendations for patients using immunosuppressive drugs other than biologics and for second-line PCP treatments (atovaquone or pentamidine). Moreover, evidence for CTD-PCP is still insufficient. We used the DPC database to emphasise the coverage of cases, considering that CTD-PCP is a rare disease, and presented the treatment status and prognosis in this study. Owing to the limitation of having a small number of patients, we could not sufficiently adjust for patient background and confounding factors in each treatment group. Therefore, we must be careful in interpreting the results on survival rates; however, we would like to base the results of this study on clinical research in a future study to evaluate the effects of drug treatments.

Our study has several limitations due to the retrospective, non-randomised, observational study design. Despite the use of a nationwide database, the study cohort comprised only 333 patients. Therefore, it was difficult to adequately adjust for previously reported confounding factors in the multivariable analysis. The GC dose and type and dose of immunosuppressants, with or without prophylaxis administered at the time of PCP onset, have also been proposed as potential prognostic factors for evaluating antibiotic treatment in patients with CTD-PCP and should therefore be included as confounding factors.[27] However, the DPC database does not contain this information and hence could not be included in the adjustment of patient background characteristics.[28 29] One approach to overcome this limitation would be to adjust the background characteristics after matching the DPC data with the National Database of Health Insurance Claims data. The DPC database, which contains medical information during hospitalisation, and the National Database of Health Insurance Claims database, which contains medical information, such as prescription drugs in outpatient settings, were treated as separate databases. As there are many institutional, technical and ethical issues in the identification of individuals and linking of both databases, we could not link the databases from which we sampled the data in this study from 2014 to 2016. If future institutional changes and technological innovations permit us to link the databases before and during hospitalisation, we would like to investigate the linking of individuals' data.

GCs are also used as treatments for moderate to severe PCP.[30 31] Although the administration of GCs may affect the prognosis of CTD-PCP, it was difficult to accurately identify the dosage, duration and purposes of GCs due to the limitations of the DPC database. Therefore, to avoid misleading the readers we restricted our description to whether GCs were administered or not. To resolve this limitation, we consider combining a medical record review in a future study.

Additionally, the DPC database cannot track disease course after hospital discharge or transfer of the patient to another institution. Therefore, the outcomes of patients after their transfer to hospitals other than those participating in the DPC database or after their admittance to a non-DPC-participating hospital after discharge are not known. Laboratory results, microbiological test results, imaging findings and medical records are not available in the DPC database.[32] The disease diagnoses, including comorbidities, and causes of death were based on the data extracted from the DPC database, and the diagnostic basis was not completely supported. Previous studies on PCP using the administrative or claims database diagnosed and defined PCP using ICD codes.[33 34] On the basis of these reports, we also made a diagnosis and definition based on the ICD-10 codes. We also defined them according to the antibiotics administered for PCP during hospitalisation to ensure the validity of the diagnosis. Antibiotics for treating PCP, such as high-dose ST, atovaquone and pentamidine, are unlikely to be used for infections other than PCP. Cases in which antibiotics for treating PCP have been administered for more than a certain period are considered to have a high probability of true PCP. It is reasonable to assume that patients with CTD-PCP were likely to be administered immunosuppressive therapy, because PCP occurs in immunocompromised hosts. Therefore, patients with CTD-PCP are more likely to have a definitive diagnosis of CTD. Regarding the diagnosis recorded in the DPC database, they are entered by the physician in charge of the treatment or by a specially trained medical professional under the supervision of a physician. The validity of DPC database has been reported to be moderate (eg, 68.8% sensitivity, 97.5% specificity, 75.9% positive predictive value and 96.5% negative predictive value for congestive heart failure).[35] In relatively rare diseases, such as CTD-PCP, research has been insufficient to evaluate the validity. Thus, further investigation is needed in the future.

In the present nationwide study using the DPC database, we found that CTD-PCP remained a fatal complication with a mortality rate of more than 30% and that older age and concomitant ILD were poor prognostic factors. ST might be a reasonable first-line antibiotic in CTD-PCP as well as in HIV-PCP. In patients with inadequate response to ST, if available, treatment with atovaquone might achieve good prognosis comparable to that of ST.

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