The Clinical Efficacy of Fluoroquinolone and Macrolide Combination Therapy Compared with Single Agent Therapy against Community-Acquired Pneumonia Caused by *Legionella Pneumophila*

Running title: *Legionella pneumophila* pneumonia

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Legionella pneumophila pneumonia is an acute infectious disease that causes severe pneumonia (1, 2). *Legionella* community-acquired pneumonia (CAP) has a mortality rate of 10%, which increases to 27% in patients who do not receive adequate antibiotic treatment as part of the empirical treatment on admission (3). Erythromycin has been the treatment of choice for Legionnaires disease since a retrospective study of the epidemic outbreak in Philadelphia in 1976 showed a significantly lower death rate in patients treated with this antibiotic (4). Recently, fluoroquinolones have been found to achieve high intracellular levels with a lower minimum inhibitory concentration (MIC) against *Legionella* than erythromycin, resulting in successful treatment of patients with *L. pneumophila* pneumonia (5, 6). Some clinical observations indicate that fluoroquinolones are highly effective especially for treating patients with severe illnesses or low immunosuppression (7). In addition, many physicians have opted to use a combination therapy against *L. pneumophila* pneumonia, especially in severe cases. Therefore, it is important to compare the efficacy of single-agent therapy with combination therapy. The aim of this study was to elucidate the characteristics of *L. pneumophila* pneumonia and the clinical efficacy of combination therapy compared with single-agent therapy.

This retrospective study includes patients with CAP caused by *L. pneumophila* who

were admitted to the Nagasaki University Hospital and 7 affiliated hospitals from April 1, 1999, to March 31, 2008. Data for each patient were collected from databases and medical records. Results are expressed as the mean value ± standard deviation. Statistical analysis was performed by using Statview statistics software version 5.0. The mean values were compared using the Mann-Whitney U test. Proportions were compared using the $\chi 2$ test with Yates correlation.

Out of a total of 22 patients, 18 (81.8%) received a urinary antigen test; 16 (88.9%) of which had a positive result. Fifteen (68.2%) of the 22 patients had a history of smoking, with an average smoking index of 799.3 ± 435.9. Fourteen (63.6%) of the 22 patients had underlying diseases, such as diabetes mellitus in 6 patients and pulmonary emphysema in 4 patients. In the laboratory findings at the time of admission, consistent with previous reports, the lactate dehydrogenate (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), serum creatinine (Cr), and aspartate aminotransferase (AST) were increased in the present study. Moreover, the average partial pressure of arterial oxygen (PaO_2) on admission was decreased (62.7 ± 12.6 torr), and the arterial alveolar oxygen tension gradient was increased ($AaDO_2$) (48.8 ± 12.9 torr). In the chest radiographs manifestation, the average chest X-ray score was 5.0 ± 2.1. 15 (68.2%) cases showed consolidation alone. The average of P/F ratio and $AaDO_2$ was 225.95 ±

110.5, 42.3 ± 4.5, respectively. 7 (27.3%) cases showed consolidation with interstitial shadow. The average of P/F ratio and $AaDO_2$ was 177.7 ± 73.2, 55.2 ± 6.1, respectively. We noted statistically significant relationships between the presence of an interstitial shadow and abnormalities in the P/F ratio ($P<0.05$) and $AaDO_2$ ($P<0.05$). In the treatment, we compared the treatment regimens (fluoroquinolone alone, macloride alone, and fluoroquinolone with macrolide) to clarify their clinical efficacy. Table 1 shows the background and outcome for each group. Although the average pneumonia severity index (PSI) score was higher in the combination group, the outcome was not significantly different as compared to the single-agent therapy groups. We also compared the clinical course of these 3 regimens by determining the degree of improvement on the 3rd and 7^{th} treatment days. As shown in Table 2, on the 3rd treatment day, the clinical status was progressive or showed poor improvement even if the anti-legionella drugs were selected correctly. Conversely, after the 7th treatment day, the clinical status was improved dramatically, especially in patients who received combination therapy; no statistical significance in patient outcome was found among the 3 regimens.

Multimodality therapy, such as the combination of antimicrobials, corticosteroids, and sivelestat sodium, is generally considered for *L. pneumophila* pneumonia. However,

there is no evidence to support the clinical efficacy of multimodality therapy. Several case studies have described the successful treatment of *L. pneumophila* pneumonia with fluoroquinolones (8, 9). Clinically, many physicians tend to use a combination therapy against *L. pneumophila* pneumonia, especially in severe cases. Therefore, it is important to compare the efficacy of single-agent therapy with combination therapy. Although Martin et al reported that a combination of ciprofloxacin and clarithromycin show a synergistic effect against *Legionella* species *in vitro* (10, 11), there has been no study comparing the clinical efficacy of combination therapy with fluoroquinolones and macrolides. In the present study, we retrospectively compared the clinical effects of single-agent therapies, fluoroquinolones and macrolides, with combination therapy in the treatment of *L. pneumophila* pneumonia. Although each treatment resulted in little or no improvement by the 3rd treatment day, the clinical course was improved greatly by the 7th treatment day, especially in the combination therapy group; nevertheless. The reason for early improvement in the group treated with fluoroquinolones and macrolide might be related to the immunomodulatory effects of macrolides (12, 13). In Western countries, new macrolides and fluoroquinolones, such as azithromycin, levofloxacin, and moxifloxacin, are recommended for treating *L. pneumophila* pneumonia (2, 14). However, the complications and mortality rate in patients with *L. pneumophila*

pneumonia depend on the administration timing of appropriate antimicrobial therapy and the presence of immunosuppression, the severity of the underlying diseases, and the severity of the pneumonia (2, 15). The advantages of choosing macrolides, fluoroquinolones , or both for *L. pneumophila* pneumonia in healthy patients or CAP may only be those reported in this study: shorter time to apyrexia and thus a more rapid achievement of good health status. In these patients, complications and mortality are probably not influenced by the choice of either type of drug and combination therapy. Nevertheless, sufficient information currently supports the use of combination therapy in severe cases of *L. pneumophila* pneumonia (16). In conclusion, fluoroquinolone combined with macrolide may be able to improve the inflammation caused by *Legionella pneumophila* pneumonia earlier than single agent therapy although there were no significant differences in outcome. However, this study had small numbers of patients and it is difficult to draw conclusion. A larger population sample is needed to definitively determine the treatment that is most effective for *L. pneumophila* pneumonia.

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Table 1.
Clinical differences between single-agent therapy and combination therapy

		Total (n=22)	Fluoroquinolone alone (n=12)	Macrolide alone (n=4)	Fluoroquinolone +macrolide (n=6)
PSI score	II	6	6	0	0
	III	7	1	2	3
	IV	5	2	2	2
	V	4	3	0	1
Average		3.3 ± 1.2	3.2 ± 1.3	3.5 ± 4.1	3.6 ± 0.8
Fluoroquinolones		18			
Ciprofloxacin		15	10	-	5
Pazufloxacin		3	2	-	1
Combination					
Corticosteroid		6	3	0	3
Sivelestat		4	1	0	3
Ventilation		6	2	0	4
Dialysis		3	2	0	1
Duration of antibiotics (days)		12.8 ± 4.3	12.9 ± 3.6	14.8 ± 3.5	12.8 ± 6.0
Hospitalization length (days)		33.6 ± 20.9	29.6 ± 16.3	32.3 ± 21.7	33.3 ± 27.8
Deaths (mortality rate; %)		2 (9.1%)	1 (8.3%)	0 (0%)	1 (16.7%)

Table 2.
Comparison of the improvement rate (%) at 3 treatment days and 7 treatment days between single-agent therapy and combination therapy

	Total (n=22)		**Fluoroquinolone alone (n=12)**		**Macrolide alone (n=4)**		**Fluoroquinolone +macrolide (n=6)**	
Parameter	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**
WBC ($\times 10^3/mm^3$)	13.0	10.9	17.9	2.1	18.1	4.2	4.9	81.2*
CRP (mg/dl)	28.1	61.8*	9.5	48.4*	6.2	29.4*	20.3	80.5*
P/F ratio	-9.0	34.7*	1.1	28.8*	-0.8	16.1*	9.1	38.4*
Decrease in body temperature (°C)	0.59	1.2	0.05	1.35	0.03	0.9	0.1	1.4
Chest X-ray score	-21.9	31.3*	-25.4	28.9*	-30.4	23.2*	-20.5	41.5*

*P<0.05; improvement rate (%), day0 (admission day) to day 3 versus day3 to day 7