Efficacy of Azithromycin for Treatment of Acute Exacerbation of Chronic Fibrosing Interstitial Pneumonia: A Prospective, Open-Label Study with Historical Controls

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Key Words

Acute exacerbation · Azithromycin · Chronic fibrosing interstitial pneumonia · Idiopathic pulmonary fibrosis

Abstract

Background: Acute exacerbation of chronic fibrosing interstitial pneumonia (AE-CFIP) is an often fatal condition with no established treatment. Recently, macrolides were found to be beneficial in cases of acute lung injury. **Objectives:** To examine the clinical effectiveness and safety of intravenous azithromycin in patients hospitalized for AE-CFIP. **Methods:** A prospective, open-label study with historical controls was conducted. Twenty consecutive patients with AE-CFIP received azithromycin. They were compared with a historical cohort treated with fluoroquinolone (n = 56). All patients received high-dose steroid pulse therapy. The primary end point was mortality at 60 days. The secondary end point was safety of intravenous azithromycin in patients with AE-CFIP. Inverse probability of treatment weighting (IPTW) using the propensity score was performed to investigate the relationship between azithromycin use and survival time. **Results:** Mortality was significantly lower in the patients treated with azithromycin than in those treated with fluoroquinolone (mortality rate at 60 days: 20 vs. 69.6%, $p < 0.001$; median

survival time: not reached vs. 29.5 days, $p < 0.001$). The IPTW adjusted hazard of mortality at 60 days in patients receiving azithromycin was 0.17 (95% CI 0.05–0.61). No serious adverse events were observed. **Conclusions:** Azithromycin was associated with improved outcomes in patients with AE-CFIP. Further studies are needed to verify this finding (Clinical trial JMA-IIA00095).

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing lung disease [1]. Some patients with IPF show acute respiratory deterioration, defined as acute exacerbation (AE) [2]. Studies have shown that AE is not unique to IPF and also occurs in other types of chronic fibrosing interstitial pneumonia (CFIP), such as nonspecific interstitial pneumonia (NSIP) [3] and chronic hypersensitivity pneumonitis (CHP) [4]. There is no established treatment for AE of CFIP (AE-CFIP). However, in clinical practice, most patients are treated with broad-spectrum antibiotics in addition to high-dose steroids, because infection, particularly atypical pneumonia, cannot be excluded. Previously, when we encountered a patient with

AE-CFIP, we used fluoroquinolone in addition to high-dose steroids. Recently, macrolides have been reported to reduce mortality in acute lung injury [5]. Therefore, the efficacy of intravenous azithromycin, a member of the macrolide class of antibiotics (which inhibit bacterial RNA-directed protein assembly), was prospectively evaluated, and the results were compared with historical data from patients with AE-CFIP who were treated with fluoroquinolone at our institution.

Methods

Study Design and Patients

The study subjects included 2 cohorts of patients with AE-CFIP, one of which received intravenous azithromycin (prospective cohort) and the other fluoroquinolone (historical cohort) as the initial treatment in a single center, a 400-bed tertiary hospital in Kumamoto, Japan.

Our hospital plays a central role in treating emergency patients in the surrounding area and is one of the referral centers in this area for interstitial lung disease. About 200 patients with interstitial pneumonia (IP) are seen per year in the outpatient department. The annual incidence of AE is 5–10 cases per year (rate 2.5–5% per year), and around 5–10 patients are transferred to our hospital because of AE of IP from other hospitals every year. Thus, 10–20 patients with AE of IP were treated per year between 2008 and 2013. The major causes of acute worsening are: AE (approx. 40%), infection (approx. 30%), induced by drugs (>10%), heart failure (>5%) and pneumothorax (>5%). All patients in this study were admitted to the hospital as an emergency or were referred to our hospital due to acute worsening of respiratory failure.

Eligible patients had a clinical diagnosis of CFIP, including IPF, fibrosing NSIP or CHP. IPF and NSIP were defined by consensus criteria [1, 6]. CHP was defined as previously described [7]. Some patients with fibrosing NSIP (n = 9) and CHP (n = 1) who refused surgical lung biopsy were diagnosed clinically, based on high-resolution computed tomography (HRCT), bronchoalveolar lavage findings, medical interview regarding putative antigen exposure, clinical data and physical examination. Patients with AE-CFIP associated with collagen vascular disease and those who were on chemotherapy for malignancy or drugs known to cause pulmonary toxicity were excluded. The primary outcome was mortality at 60 days after admission. The secondary outcome was safety of intravenous azithromycin in patients with AE-CFIP.

The institutional review board of our hospital approved the study. All patients provided their written, informed consent in accordance with the Declaration of Helsinki (Clinical trial registration JMA-IIA00095).

Acute Exacerbation

AE was defined as outlined by the Japanese Respiratory Society Criteria [8] with minor revisions: (1) previous or concurrent diagnosis of FIP, (2) unexplained worsening or development of dyspnea within the previous 30 days, (3) HRCT scan with new bilateral ground-glass and/or consolidation superimposed on a background with reticular or honeycombing characteristics, (4) worsening hypoxia relative to a known baseline arterial blood gas,

(5) elevations of serum KL-6 and serum lactate dehydrogenase (LDH) levels and (6) exclusion of other known causes of exacerbation, such as pulmonary infection, pneumothorax, aspiration, malignancy, pulmonary thromboembolism and heart failure. To exclude infection, cultures of sputum, blood and urine, *Streptococcus pneumoniae* and *Legionella* urinary antigen tests, rapid influenza diagnostic testing and a beta-D-glucan assay were conducted for all patients. Bronchoalveolar lavage and endotracheal aspiration were not routinely performed because of severe respiratory failure. Cytomegalovirus antigenemia testing was carried out in patients who had received long-term high-dose prednisone and/or immunosuppressant treatment. Measurement of serum B-type natriuretic peptide levels and echocardiography were performed to assess whether respiratory failure was cardiogenic.

Azithromycin Cohort (Prospective Group)

Exclusion criteria regarding azithromycin use prior to the study were defined. The exclusion criteria were: (1) macrolide allergy or intolerance and (2) risk factors for adverse effects of azithromycin, including (1) corrected QT interval of more than 450 ms and (2) a history of prolonged QT syndrome. No patient was excluded on the basis of these criteria.

A total of 22 patients with AE-CFIP were treated from 1 July 2012 to 30 June 2013. Two patients were excluded, 1 with a collagen vascular disease and 1 receiving chemotherapy for malignancy. A total of 20 patients with AE-CFIP who met the above-mentioned criteria were prospectively enrolled and treated by azithromycin. Administration of azithromycin was started when the patients fulfilled the AE criteria. All patients received 500 mg of intravenous azithromycin for 5 consecutive days. Demographics, clinical features, clinical data on admission, medication history, HRCT data and other therapeutic interventions were obtained for all patients. The extent of honeycombing on HRCT was calculated as previously described [9].

The patients were followed up until the primary end point or 60 days from admission.

Selection of treatment options (i.e. whether or not to perform mechanical ventilation or repeat high-dose steroid pulse therapy) was at the discretion of the attending physician, but the combined use of fluoroquinolone and azithromycin was restricted.

Fluoroquinolone Cohort (Historical Cohort)

Seventy-three patients with AE-CFIP were identified retrospectively from longitudinal cohorts of patients with CFIP at our hospital from April 2005 to June 2012. The patients were re-evaluated with respect to fulfillment of the above-mentioned criteria. Seventeen patients were excluded because of evidence of collagen vascular disease-associated IP (n = 9), possible drug-induced pneumonia (chemotherapy, n = 2), possible infection (n = 3), possible aspiration (n = 2) and possible heart failure (n = 1). A total of 56 patients were included in this study. All patients in this cohort provided written, informed consent to record their clinical data and review their medical records.

Demographics, clinical features, clinical data, medication history, HRCT data, therapeutic interventions and 60-day mortality were retrospectively collected for all patients.

Statistical Analysis

Baseline characteristics in each treatment group were summarized using percentages for categorical variables and means and standard deviations for continuous variables. Comparisons be-

tween groups were performed using the Mann-Whitney rank-sum test and the Fisher exact test, respectively. Survival time (in days) is reported as median (95% CI), calculated from admission until mortality from any cause within the study periods. Patients were censored if they were alive at 60 days. Survival curves were plotted using Kaplan-Meier methods. Log-rank tests were used to compare differences in survival.

Unadjusted and adjusted Cox regression modeling was performed. The adjusted model was performed using stepwise selection of variables based on the Akaike information criterion. Variables included age, sex, clinical diagnosis (IPF or non-IPF), biopsy, extent of honeycombing on HRCT, prednisolone and immunosuppressant use prior to admission, APACHE II (Acute Physiology and Chronic Health Evaluation II) score, serum KL-6 level, serum LDH and serum C-reactive protein level at admission, as previously reported [10–14].

Adjusted relationships between treatment and outcome were estimated using Cox proportional-hazards regression using 5 variables (age, immunosuppressant use, diagnosis of IPF, use of mechanical ventilation and use of azithromycin).

Adjusted relationships between treatment and outcome were also estimated using the Cox proportional-hazards regression model via inverse probability of treatment weighting (IPTW) using the propensity score [15]. The weights were based on the probability of receiving azithromycin. Logistic regression models were used to estimate the propensity to receive azithromycin versus no azithromycin. The model included all of the above-mentioned variables. All tests were two-sided and were performed at a significance level of $p = 0.05$. The R statistical package (version 3.0.1; The R Foundation for Statistical Computing) was used for all analyses.

Results

Study Population

The study cohort consisted of 76 patients (56 historical, 20 prospective). Comparison of the baseline clinical characteristics between the azithromycin and fluoroquinolone groups is shown in table 1.

There were no significant differences between the 2 groups in terms of age, sex, clinical diagnosis of CFIP, surgical lung biopsy, presence and extent of honeycombing on HRCT, blood test results, APACHE II score and corticosteroid and immunosuppressant use before AE.

Therapeutic interventions performed during the study are listed in table 2. There was no significant difference in therapeutic interventions between the 2 groups. Invasive mechanical ventilation tended to be more frequently performed in the fluoroquinolone than in the azithromycin group, but this difference was not significant ($p = 0.053$).

Effect of Treatment on Mortality

There were 4 deaths due to respiratory failure following AE in the azithromycin group and 39 deaths (38 due to respiratory failure and 1 due to aortic dissection) in the

Table 1. Summary of baseline characteristics of the study cohorts

Variable	Azithromycin (n = 20)	Fluoroquinolone (n = 56)	p value
Age, years	74.4±9.5	73.2±9.7	0.75
Sex, female	3 (15)	16 (28.6)	0.37
Clinical diagnosis			0.07
IPF	16 (80)	39 (70)	
Fibrotic NSIP	2 (10)	16 (29)	
CHP	2 (10)	1 (2)	
Biopsy	3 (15)	14 (25)	0.53
Honeycombing on HRCT	18 (90)	39 (70)	0.08
Extent of honeycombing (n = 57), %	12.0±6.4	9.1±6.0	0.11
KL-6, U/ml	2,006±1,517	1,556±1,353	0.11
SP-D (n = 69), ng/ml	482±442	500±394	0.52
LDH, IU/l	396.9±123.8	366.9±129.3	0.28
C-reactive protein, mg/dl	8.0±5.9	6.4±4.3	0.42
APACHE II score	15.9±3.6	15.7±4.0	0.93
PaO ₂ /FiO ₂ , mm Hg	176.1±91.2	153.1±77.2	0.45
Treatment before admission			
Prednisolone	13 (65)	30 (54)	0.44
Immunosuppressant	2 (10)	17 (30)	0.08

SP-D = Surfactant protein D.

Table 2. Therapeutic interventions and outcome and cause of death in the study cohorts

Intervention and outcome	Azithromycin (n = 20)	Fluoroquinolone (n = 56)	p value
High-dose steroid pulse	20 (100)	56 (100)	1
Combination with			
beta lactam	1 (5)	5 (8.9)	1
IMV	0 (0)	9 (16) ^a	0.053
NIMV	7 (35)	27 (48)	0.43
PMX	0 (0)	2 (3.5)	1
DNAR	7 (35)	16 (28.6)	0.58
60-day deaths	4 (20)	39 (69.6)	<0.001
Cause of death			
Respiratory failure	4 (100)	38 (97.4)	1
Aortic dissection	0 (0)	1 (2.6)	1

Figures in parentheses are percentages. DNAR = Do not attempt resuscitation; IMV = invasive mechanical ventilation; NIMV = non-invasive mechanical ventilation; PMX = polymyxin B-immobilized fiber column-direct hemoperfusion.

^a Seven patients had NIMV before IMV.

fluoroquinolone group, and the difference was significant ($p < 0.001$; table 2).

Patients with AE-CFIP treated with azithromycin had significantly better survival than patients treated with fluoroquinolone (crude Kaplan-Meier survival analysis; $p <$

Table 3. Unadjusted and adjusted predictors of survival time

Variable	Unadjusted			Adjusted ^a		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.03	(0.99–1.06)	0.11	1.03	0.99–1.07	0.07
Male sex	0.76	(0.40–1.46)	0.41			
Clinical diagnosis IPF	0.73	(0.39–1.37)	0.33			
Biopsy	0.96	(0.47–1.94)	0.9			
Extent of honeycombing	0.98	(0.94–1.03)	0.56			
Prednisolone	0.94	(0.51–1.73)	0.84			
Immunosuppressant	1.46	(0.77–2.76)	0.25	1.87	0.9–3.89	0.09
APACHE II	1.1	(1.02–1.18)	0.02			
KL-6	1	(0.99–1)	0.88			
SP-D (n = 67)	1	(0.99–1)	0.18			
LDH	1.002	(1–1.005)	0.05			
C-reactive protein	1.04	(0.99–1.09)	0.1			
MV	1.34	(0.74–2.44)	0.39			
PaO ₂ /FiO ₂ ratio	1	(0.99–1)	0.08	0.99	0.99–0.99	0.02
Azithromycin use	0.21	(0.07–0.58)	0.003	0.22	0.08–0.61	0.004

MV = Mechanical ventilation (invasive + noninvasive); SP-D = surfactant protein D.

^a Using stepwise selection of variables based on the Akaike information criterion.

Fig. 1. Unadjusted Kaplan-Meier survival curves for the patients with AE-CFIP treated with azithromycin or fluoroquinolone.

0.001). The median survival time (MST) was 29.5 days in the fluoroquinolone group. The azithromycin group had not reached the median survival at the last follow-up (fig. 1).

Predictors of Survival

Unadjusted predictors of survival are listed in table 3. APACHE II score, serum LDH and azithromycin use were all associated with survival. On adjusted analysis, a higher PaO₂/FiO₂ ratio and the use of azithromycin were

Table 4. Cox proportional hazards model results for azithromycin use and mortality

Model	HR	95% CI	p value
Unadjusted	0.21	0.07–0.58	0.003
Multivariable adjusted ^a	0.22	0.08–0.61	0.004
Multivariable adjusted ^b	0.21	0.07–0.59	0.003
IPTW	0.17	0.05–0.61	0.006

^a Using stepwise selection of variables (see table 3) based on the Akaike information criterion.

^b Adjusted for age, diagnosis of IPF and the use of mechanical ventilation, immunosuppressants or azithromycin.

associated with longer survival time in the regression model (tables 3, 4).

IPTW estimators with propensity score adjustment showed that azithromycin use was associated with longer survival (HR 0.17 and 95% CI 0.05–0.61; table 4).

Adverse Events

During the study period, there were no serious adverse events that were considered to be related to the study, and no patients had to discontinue treatment. Paroxysmal supraventricular tachycardia requiring an adjustment of heart rate was observed in 1 patient during the prescription period of azithromycin. This patient had a history of angina, and the cause-and-effect relationship between administration of azithromycin and arrhythmia was unclear.

Discussion

This study showed that intravenous azithromycin (500 mg/day for 5 days) was associated with an improved outcome in patients with AE-CFIP without serious adverse events.

In the study patients with AE-CFIP, 60-day mortality was significantly lower with azithromycin than with fluoroquinolone treatment. Previous retrospective studies reported a mortality rate of AE-IPF of 50–90% [10, 12, 16, 17]. We previously reported an MST of 0.9 months and a mortality rate of 86% in AE-IPF [18]. Recently, a retrospective, multicenter analysis by Japanese groups reported an MST of approximately 1.5 months in patients with AE-CFIP treated with polymyxin B hemoperfusion. Song et al. [12] reported that the MST of AE-IPF patients was 2.2 months. The survival results of

the historical cohort (i.e. patients treated with fluoroquinolone) are comparable to these previous reports. Therefore, we suggest that the discrepancy in survival between the 2 cohorts in our study was due to improved survival with azithromycin rather than worse survival with fluoroquinolone, because no marked changes in treatment strategy in AE, particularly drug selection, were adopted by our team, except for the introduction of azithromycin.

We suggest that the survival benefit of azithromycin in AE-CFIP, if real, is due to anti-inflammatory and immunomodulating effects rather than antimicrobial activity. Fluoroquinolone and azithromycin have similar atypical pathogen activity, which denotes that the survival benefit of azithromycin in AE-CFIP is unlikely due to antimicrobial activity. Macrolides have been shown to prevent the production of proinflammatory mediators, cytokines and reactive oxygen species in vitro and in vivo in many studies [19], and they have the effect of controlling exacerbations of underlying respiratory diseases such as asthma, bronchiectasis, panbronchiolitis and cryptogenic organizing pneumonia [20]. Walkey and Wiener [5] recently proposed that the anti-inflammatory and immunomodulatory effects of macrolides may benefit patients with acute lung injury.

In this study, the AE-CFIP patients were treated with combination high-dose corticosteroids and azithromycin. Whether there is a synergistic effect between corticosteroids and azithromycin remains unclear. However, Damjanovic et al. [21] recently reported that combined treatment with azithromycin and corticosteroids had superior effects in clinical outcome, bacterial clearance, cellular and cytokine responses and immunopathological findings compared with monotherapy with these drugs in a murine model of acute lung injury triggered by viral and bacterial superinfection. The previous study used an infectious acute lung injury model, so the results may not be directly applicable to AE-CFIP. Further research is required to clarify the possibility of a synergistic effect in patients with AE-CFIP.

This study addressed the safety of a 5-day course of intravenous azithromycin in patients with AE-CFIP. There were no serious adverse events that were considered related to the study, and no patients had to discontinue treatment. Recent work has suggested an association between azithromycin use and cardiovascular events, particularly in the elderly [22, 23].

Ray et al. [22] reported that patients with a high risk for cardiovascular disease had an estimated 245 additional cardiovascular deaths per 1 million courses of azithro-

mycin treatment. Considering the high mortality rate in AE-CFIP, we suggest that the survival benefit of azithromycin use outweighs the risk of cardiovascular death in patients with AE-CFIP. However, this study included only 20 patients, so further research on safety in large populations is warranted.

The optimal duration of azithromycin therapy in patients with AE-CFIP is unknown. We selected an azithromycin course length of 5 days on the basis of a previously reported median duration of macrolide use in acute lung injury of 4 days [5]. It is also not known whether macrolides other than azithromycin have similar beneficial effects in AE-CFIP. Further study is needed to clarify these points.

Our study had several limitations. First, it was a non-blinded study and it included retrospective data. There might have been an improvement in supportive care over the 7 years, and there might always be a possibility that more attention was paid to the prospective study group. There may also be the possibility of missing cases in the retrospective control group, especially less sick patients. Second, the sample size was small, especially the azithromycin group, which greatly increases the risk of random error. We adjusted for overt biases by applying IPTW using propensity scores [15] to resolve problems created by unequal chances of receiving treatment. However, we still cannot rule out the possibility that unmeasured confounding factors might have af-

fected our results, and that fluoroquinolones might have a potentially harmful effect on AE-CFIP. Due to these potential limitations, the data should be interpreted with caution. However, since there is no established treatment for AE of IP, a randomized, clinical trial of the use of AZM in AE-CFIP should be encouraged. Third, because of the limited sample size, the study did not analyze the details of any adverse effects of intravenous azithromycin therapy in patients with AE-CFIP. Fourth, we do not routinely perform bronchoalveolar lavage to exclude infection at the diagnosis of AE or virus tests, except for influenza testing, so the possibility of mixed viral and atypical pathogen infection could not be ruled out.

In conclusion, the results of this study suggest that the administration of intravenous azithromycin may increase survival in patients with AE-CFIP. However, for confirmation of this finding, a prospective, randomized, controlled study is warranted.

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