Retrospective Analysis of Azithromycin Versus Fluoroquinolones for the Treatment Of *Legionella* Pneumonia

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ABSTRACT

Background: *Legionella* is often associated with life-threatening pneumonia that is responsible for significant morbidity and mortality. Fluoroquinolones (FQ) have demonstrated improved clinical outcomes or decreased complications compared with clarithromycin and erythromycin. However, there is limited data comparing outcomes of FQ to azithromycin (AZM), which exhibits better *Legionella* activity than erythromycin and clarithromycin.

Methods: This single-center retrospective study compared clinical outcomes of patients with *Legionella* pneumonia (LP) treated with AZM versus FQ from January 1999 to May 2011.

Results: A total of 41 patients were included in the analysis; 21 received FQ and 20 received AZM. Demographics, comorbidities, and disease severity were similar between groups. Mortality (9.5% vs. 5%, $P > 0.99$), time to clinical stability (15.89 days vs. 10.26 days, $P = 0.09$), length of hospitalization (19.29 days vs. 11.35 days, $P = 0.06$), and presentation of any complication (85.7% vs. 90%, $P > 0.99$) were similar between the FQ and AZM groups, respectively.

Conclusion: Azithromycin appears to have clinical efficacy similar to FQ for the treatment of *Legionella* pneumonia.

Key Words: *Legionella pneumophilia*, Legionnaires' disease, macrolides, azithromycin, levofloxacin, community-acquired pneumonia

INTRODUCTION

Legionella is a gram-negative bacterium that replicates within alveolar macrophages and is commonly found in soil, fresh water, and man-made water systems, such as cooling devices associated with air conditioning.[1–2] The most common serotype in North America is *Legionella pneumophilia* type 1, which is implicated in 80% to 95% of cases of *Legionella* pneumonia (LP).[3–4] *Legionella*, a commonly reported cause of severe sporadic and epidemic community-acquired and nosocomial pneumonias, has been identified as one of the major pathogens in patients with community-acquired pneumonia (CAP) who require admission to the intensive care unit (ICU).[5–6] The incidence of LP is higher than previously thought and has been increasing over the last decade, with at least 13,000 cases occurring annually.[6–7] Additionally, the incidence of LP increased nearly threefold from 2001 to 2009.[7] Rates of underdiagnosis and underreporting are high; it has been estimated that only 2% to 10% of LP cases are reported.[5,7] Signs and symptoms of LP are relatively nonspecific and *Legionella* species are fastidious and difficult to culture, thereby making diagnosis and targeting of specific treatment more difficult.[1,7]

Macrolides and fluoroquinolones (FQ) exhibit *in vitro* activity against *Legionella pneumophilia*, but retrospective comparator studies indicate improved clinical outcomes or reduced complication rates with FQ compared to macrolides.[5,8] However, the macrolides evaluated in these studies were erythromycin and clarithromycin, which are less active or inferior to azithromycin (AZM) in pharmacokinetic and animal studies.[8–11] *In vitro* tests, animal models, and cell culture studies suggest AZM's antibiotic activity against *Legionella* is comparable to FQ, but there are limited data comparing clinical outcomes in patients with LP.[9–16] Additionally, AZM has a favorable safety profile, lower minimum inhibitory concentrations, higher intracellular concentrations, and longer postantibiotic effect than erythromycin and clarithromycin in pharmacokinetic and animal studies.[13] Thus, similar efficacy and safety among the macrolide class should not be assumed when treating LP. The objective of this analysis was to evaluate clinical outcomes and complications of AZM versus FQ for the treatment of LP.

METHODS

This retrospective, single-center study compared the clinical outcomes of adult patients (18 years and older) receiving AZM or FQ for the management of LP and was approved by the University of Michigan Institutional Review Board. Patients with a clinical diagnosis of pneumonia (defined as radiologic evidence of pneumonia and symptoms consistent with pneumonia) and a positive *Legionella* urinary antigen test (Binax Now, Alere) between January 1999 and May 2011 were screened for inclusion. Patients were excluded if they had been transferred from an outside hospital with incomplete medical records, had received erythromycin or clarithromycin, or had received combination therapy with AZM and FQ.

Patients were categorized in the FQ or AZM group based on which antibiotic they received following the positive *Legionella* antigen test. Clinical outcomes measures included: 30-day

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all-cause mortality, length of hospitalization, time to clinical stability (defined as normalization of vital signs and oxygenation for at least 24 hours), and development of complications (respiratory failure, hemodynamic instability requiring vasopressor therapy, acute renal failure, and hepatotoxicity). Clinical stability was defined as a return to baseline vital signs for heart rate, respiratory rate, and oxygen requirement for patients on home therapy. Additionally, time to clinical stability included time until defervescence, defined as temperature less than 38 degrees Celsius. GraphPad Prism 6 (GraphPad Software Inc.), was used to perform statistical calculations. Categorical data were evaluated using the chi-square test or Fisher's exact test. Continuous data were analyzed using the Student's t-test. Significance was established at a *P* value less than or equal to 0.05.

RESULTS

A diagnosis of *Legionella* pneumonia was identified for 49 patients, and 41 patients were included in the final analysis: 21 in the FQ group and 20 in the AZM group. Eight patients received combination *Legionella* therapy or were transferred from an outside hospital with incomplete medical records and were excluded. Baseline characteristics were generally similar between groups (Table 1). However, a significantly higher percentage of patients in the AZM group had cardiovascular disease (FQ, 4.8% [1/21]; AZM, 35% [7/20]; $P = 0.02$). Antibiotic treatment prior to admission with a macrolide (FQ, 14% [3/21]; AZM, 10% [2/20]; $P = 1.0$), or FQ (FQ, 14% [3/21]; AZM, 0% [0/20]; $P = 0.23$) was similar and infrequent in both groups. Clinical outcomes and complications were not different between groups (Table 2). Direct admission to the ICU was similar between groups (FQ, 47.6% [10/21]; AZM, 25% [5/20]; $P = 0.14$). The overall number of patients admitted to the ICU at any time during hospitalization was 14 in the FQ group and nine in the AZM group ($P = 0.21$), and more patients in the FQ cohort received mechanical ventilation (FQ, 67% [14/21]; AZM, 35% [7/20]; $P = 0.06$). The mean APACHE III score was also similar among ICU patients in both groups (FQ, 81.93 ± 24.60; AZM, 69.00 ± 22.01; $P = 0.47$).

Mortality (FQ, 9.5% [2/21]; AZM, 5% [1/20]; $P > 0.99$), time to clinical stability (FQ, 15.89 days; AZM, 10.26 days; $P = 0.09$), and length of hospitalization (FQ, 19.29 days; AZM, 11.35 days; $P = 0.06$) were not statistically different between groups. Outcomes for patients directly admitted to the ICU were also similar between groups: mortality (FQ, 20% [2/10]; AZM, 20% [1/5]; $P > 0.99$), time to clinical stability (FQ, 25.3 ± 12.4 days; AZM, 17.6 ± 6.8 days; $P = 0.24$), and length of ICU stay (FQ, 14.57 ± 8.03 days; AZM, 11.89 ± 7.15 days; $P = 0.42$).

Table 1 Patient Demographics

	Fluoroquinolones (n = 21)	Azithromycin (n = 20)	*P* value
Age (years)*	50.67 ± 15.22	52.65 ± 13.48	0.66
Males	14	10	0.35
Antibiotic use prior to admittance			
Macrolide	3/21 (14%)	2/20 (10%)	1.0
Fluoroquinolone	3/21 (14%)	0/20 (0%)	0.23
Direct admission to ICU	10 (47.6%)	5 (25%)	0.2
Alcohol use	6/21 (29%)	5/20 (25%)	1.0
Tobacco use	12/21 (57%)	10/20 (50%)	0.76
Chronic pulmonary disease	2/21 (9.5%)	1/20 (5%)	1.0
Diabetes	5/21 (24%)	4/20 (20%)	1.0
Cardiovascular disease	1/21 (4.8%)	7/20 (35%)	0.02
Chronic kidney disease	3/21 (14%)	3/20 (15%)	1.0
Chronic liver disease	2/21 (9.5%)	1/20 (5%)	1.0
Transplant	1/21 (4.8%)	1/20 (5%)	1.0
Cancer	3/21 (14%)	4/20 (20%)	0.70
Chronic steroid use	2/21 (9.5%)	1/20 (5%)	1.0
Immunosuppression	4/21 (19%)	1/20 (5%)	0.34
Positive *Legionella* sputum culture	3/21 (14%)	1/20 (5%)	0.61
APACHE III score*	81.93 ± 24.60	69.00 ± 22.01	0.47

*mean ± standard deviation

Table 2 Clinical Outcomes and Complications

	Fluoroquinolones (n = 21)	Azithromycin (n = 20)	*P* value
Clinical Outcomes			
Mortality			
All patients	2/21 (9.5%)	1/20 (5%)	> 0.99
ICU patients	2/10 (20%)	1/5 (20%)	> 0.99
Time to clinical stability*			
All patients	15.89 ± 12.05	10.26 ± 6.96	0.09
ICU patients	25.3 ± 12.4	17.6 ± 6.8	0.24
Length of hospitalization*			
Length of stay for all patients	19.29 ± 16.62	11.35 ± 7.49	0.06
ICU length of stay	14.57 ± 8.03	11.89 ± 7.15	0.42
Duration of mechanical ventilation*	12.79 ± 7.40	10.13 ± 7.72	0.43
Complications			
Acute renal failure	12/21 (57%)	10/20 (50%)	0.76
Dialysis	5/21 (24%)	5/20 (25%)	> 0.99
Transaminase elevation	14/21 (67%)	11/20 (55%)	0.53
Pleural effusion	10/21 (48%)	6/20 (30%)	0.34
Respiratory failure	17/21 (81%)	16/20 (80%)	> 0.99
Vasopressor use	7/21 (33%)	7/20 (35%)	> 0.99

*mean ± standard deviation

The development of any complication (respiratory failure, hemodynamic instability requiring vasopressor therapy, acute renal failure, and hepatotoxicity) was not different for the entire cohort (FQ, 85.7% [18/21]; AZM, 90% [18/20]; $P > 0.99$), and respiratory failure was the most common complication reported (FQ, 81% [17/21]; AZM, 80% [16/20]; $P > 0.99$). No differences in acute renal failure, dialysis, hepatotoxicity, pleural effusion, or vasopressor use were noted between groups.

DISCUSSION

Several studies have compared the use of the FQ levofloxacin to macrolides in the management of LP.[5,8–11]

The majority of the studies used erythromycin or clarithromycin as the comparator macrolide. Results show outcomes to be comparable with respect to clinical cure; however, use of levofloxacin was associated with shorter time to apyrexia, decreased length of hospital stay, and fewer complications.[5,8–11] One study did have a proportion of patients in the macrolide cohort who received AZM (13 of 23 patients).[10] Results of the study showed time to clinical stability and length of hospital stay were not statistically different between the two cohorts. The investigators noted a trend toward decreased length of hospital stay in the FQ cohort. Lastly, Plouffe et al. conducted an open-label trial using intravenous AZM followed by oral therapy in 25 patients diagnosed with LP.[11] The cure rate in patients who were clinically evaluable after 10 to 14 days of therapy was 95%. None of the patients in the study was reported as requiring admission to an ICU.

To our knowledge, this is the first study to compare clinical outcomes between AZM and FQ for the treatment of LP. Our results are consistent with those seen in previous trials with respect to clinical efficacy. In contrast to prior studies, however, our results do not show trends toward improved outcomes with the use of FQ. The lack of improved clinical outcomes with FQ may indicate AZM's pharmacokinetic and pharmacodynamic superiority to other macrolides for *Legionella*, or it may reflect the study's limitations, including selection bias with more critically ill patients receiving FQ. Nevertheless, our findings support recommendations for using azithromycin in the management of LP.[17]

However, several limitations should be recognized when interpreting the results. First, this study and previously published studies are retrospective and lack the appropriate sample size. This is indicative of *Legionella* pneumonia being an uncommon infection, making it difficult to perform large studies or randomized trials. Second, selection bias is possible with all retrospective single-center studies, including this study. Although demographics, comorbidities, and disease severity were not different between groups, the prescribing physician may have been more likely to prescribe AZM or FQ based on personal experience. A larger percentage of patients in the FQ group were directly admitted to the ICU, which may account for favorable trends noted in the AZM group. However, when evaluating the patients directly admitted to the ICU (who had similar APACHE III scores, respiratory failure, and vasopressor therapy between groups), there were no differences noted in mortality, ICU length of stay, or time to clinical stability.

In conclusion, this retrospective study demonstrates that clinical outcomes and complications are similar between AZM and FQ for the treatment of hospitalized patients with *Legionella* pneumonia. These results support Infectious Diseases Society of America and American Thoracic Society pneumonia guidelines, which recommend AZM and FQ as effective first-line therapy for LP.[17]

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