Background: Although fluoroquinolones possess excellent *in vitro* activity against Legionella, few large-scale clinical trials have examined their efficacy in the treatment of Legionnaires disease. Even fewer studies have applied rigorous criteria for diagnosis of community-acquired Legionnaires disease, including culture of respiratory secretions on selective media.

Methods: Data from six clinical trials encompassing 1,997 total patients have been analyzed to determine the efficacy of levofloxacin (500 mg qd or 750 mg qd) in treating patients with community-acquired pneumonia (CAP) due to Legionella.

Results: Of the 1,997 total patients with CAP from the clinical trials, 75 patients had infection with a Legionella species. Demographics showed a large portion of these patients were < 55 years of age and nonsmokers. More than 90% of mild-to-moderate and severe cases of Legionella infection resolved clinically at the posttherapy visit, 2 to 14 days after treatment termination. No deaths were reported for any patient with Legionnaires disease treated with levofloxacin during the studies.

Conclusions: Levofloxacin was efficacious at both 500 mg for 7 to 14 days and 750 mg for 5 days. Legionnaires disease is not associated only with smokers, the elderly, and the immunosuppressed, but also has the potential to affect a broader demographic range of the general population than previously thought.

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Key words: clinical efficacy; community-acquired pneumonia; Legionella; levofloxacin

Abbreviations: BCYE = buffered charcoal yeast extract; CAP = community-acquired pneumonia; ELISA = enzyme-linked immunosorbent assay; MIC = minimum inhibitory concentration; PSI = pneumonia severity index

Legionella are facultative, intracellular bacteria that penetrate and proliferate within the phagosomes of alveolar macrophages and blood monocytes.\(^1\)\(^-\)\(^3\) Thus, antimicrobials that cannot penetrate the host’s cellular membrane, such as penicillins and cephalosporins, are relatively ineffective against these bacteria.\(^4\) Legionella is a major cause of lethal pneumonia, and mortality rates range from 5 to 25% among immunocompetent hosts, and even higher among the immunosuppressed.\(^5\)

In the past, erythromycin was typically used for the treatment of Legionnaires disease. However, newer antimicrobials have been shown to be safer and more effective.\(^6\) The Infectious Diseases Society of America and the American Thoracic Society currently recommend doxycycline, azithromycin, and various fluoroquinolones for treating Legionella respiratory infections.\(^7\)\(^8\)

Levofloxacin, one of the recommended fluoroquinolones, has excellent *in vitro* activity against Legionella, with a minimum inhibitory concentration (MIC) equal to 0.03 \(\mu\)g/mL.\(^9\) In *vitro* studies\(^3\)\(^,\)\(^10\)\(^,\)\(^11\) using intracellular systems have shown that levofloxacin is effective in intracellular killing of various Legionella strains. In addition, levofloxacin concentrates in the intraalveolar compartments at levels well above the MIC.\(^12\) Steady-state concentrations of
levofloxacin in the epithelial lining fluid and alveolar macrophages are significantly higher than the plasma concentrations. The ratio of the area under the concentration-time curve or peak concentration to MIC is assumed to be a key pharmacodynamic indication for clinical and microbiologic success of the fluoroquinolones. In addition, unlike the macrolides, which are bacteriostatic for Legionella, the quinolones are bactericidal.

Legionnaires disease cannot be readily diagnosed because of its nonspecific clinical and radiologic manifestations, and the need for specialized laboratory tests. Culture and urinary antigen are considered the most specific tests for diagnosis. In the prospective analysis of levofloxacin presented herein, efficacy and toxicity data are presented for what we believe to be the largest population of cases of sporadic community-acquired Legionnaires disease ever studied.

Materials and Methods

Clinical Trials Involved

This analysis integrated data from five prospective phase III clinical trials (studies 1, 2, 3, 5, and 6) and one phase IV clinical trial (study 4). Study 1 (data on file; R.W. Johnson Pharmaceutical Research Institute; Raritan, NJ) and study 71 were open-label, noncomparative studies that evaluated the efficacy and safety profiles of levofloxacin in the treatment of CAP. Study 218 was an open-label, randomized, active-controlled study that compared levofloxacin with parenteral ceftriaxone and/or oral cefuroxime axetil in the treatment of CAP. Study 419 was an open-label, randomized, active-controlled study that compared levofloxacin with cefuroxime axetil in the treatment of CAP. Study 5 was a multicenter, randomized, double-blind study that compared the efficacy of 5-day, high-dose levofloxacin (750 mg) levofloxacin therapy with a 10-day course of levofloxacin 500 mg/d for 10 to 14 days. (Two patients in study 2 with Legionnaires disease underwent extended therapies of 15 days and 18 days, respectively.) In study 5, patients received levofloxacin, 500 mg/d, for 10 days or 750 mg for 5 days. Patients in study 6 received levofloxacin, 750 mg for 5 days. Patients in all trials were started on either IV or oral therapy, and those receiving IV therapy could be switched to oral medication at the investigator’s discretion. Clinical and microbiologic responses were determined at a posttherapy visit occurring 2 to 14 days after cessation of drug therapy, and at a poststudy visit occurring 3 to 5 weeks after the completion of drug therapy. At posttherapy, a cured or improved patient had resolution or partial resolution of clinical signs and symptoms associated with active infection, along with improvement or stabilization on chest radiograph. Failure indicated an inadequate response to therapy with additional antibiotic treatment required for the original infection. Failure was also designated for patients who had a clinical failure but in whom the admission pathogen appeared to have been eradicated (negative test-of-cure culture finding).

Legionella Diagnostic Testing

The Special Pathogens Laboratory at the VA Pittsburgh Healthcare System, Pittsburgh, PA, performed Legionella culture, urinary antigen, and serologic testing. Cases were diagnosed as Legionnaires disease based on any of the following: (1) fourfold increase in the level of IgM or IgG determined by enzyme-linked immunosorbent assay (ELISA), (2) seroconversion by the Carter Wallace IgG/IgM ELISA (Carter-Wallace-Wampole; Cranbury, NJ), (3) positive urinary antigen test result using EIA for Legionella pneumophila serogroup 1 (Binax; S.
Portland, ME), or (3) isolation of Legionella from pretreatment sputum cultures. Culture was performed using three media: buffered charcoal yeast extract (BCYE) agar; BCYE with polymyxin B, anisomycin, and vancomycin (PAV); and BCYE with polymyxin B, anisomycin, and cefamandole (PAC). Specimens were pretreated with an acid buffer (HCl-KCl, pH 2.2) for 4 min prior to plating.

**Statistical Evaluation Groups**

The intent-to-treat population consisted of all patients in the trials who were treated with levofloxacin and who fulfilled the previously mentioned criteria for CAP caused by a Legionella species. The clinically evaluable population was a combination of all Legionella-infected patients in the clinically evaluable populations of the six individual clinical trials.

**RESULTS**

**Patient Demographic and Baseline Characteristics**

From a total of 1,997 patients with a diagnosis of CAP, 75 patients (3.8%) had Legionella infection based on at least one of the following criteria: seroconversion (either fourfold increase in IgM or IgG levels determined by ELISA [55 patients] or by Wampole EIA [14 patients]), positive urinary antigen (5 patients), or positive sputum culture (6 patients). The numbers total >75 because some patients had multiple positive test results. In the clinically evaluable population, 71 of 1,551 patients (4.6%) were determined to have Legionella infection.

Patients were stratified according to the severity of the disease, with 47 patients classified with mild-to-moderate CAP and 24 patients with severe CAP. Patients were categorized according to whether they had traditional risk factors for contracting Legionella-induced CAP. Forty-six percent (33 of 71 patients) of the clinically evaluable population had a chronic respiratory disease, including bronchitis, emphysema, sinusitis, and COPD, and 41% (29 of 71 patients) had a history of smoking. Thirty-four percent (24 of 71 patients) had none of these risk factors, and over half of these (14 of 24 patients) were also <55 years of age.

Seroconversion to Mycoplasma pneumoniae and Chlamydia pneumoniae was observed in 25% (19 of 75 patients) and 17% (13 of 75 patients), respectively. Fifteen percent (11 of 75 patients) and 9% (7 of 75 patients) had Streptococcus pneumoniae and Haemophilus influenzae isolated from sputum cultures, respectively.

**Clinical Evaluations**

Seventy-one patients with community-acquired Legionnaires disease were clinically evaluable, and clinical success (cured plus improved) was observed during the posttherapy visit (Table 1) in 92.9% (66 of 71 patients) overall; 74.6% were cured and 18.3% were improved. Clinical failure occurred in five patients (7.0%) based on the criteria that additional antibiotics were prescribed by the physician. None of the five clinical failures resulted in patient death. Among the 13 patients receiving 750 mg of levofloxacin for 5 days, 12 patients (92.3%) achieved clinical success at posttherapy; 5 of the patients had severe pneumonia.

During the posttherapy visit, 93.6% of mild-to-moderate cases were assessed as clinical successes, compared with 91.6% of the severe cases. Also, no patient was found to have a documented microbiological relapse during the poststudy visit (3 to 5 weeks after therapy ended).

**Safety Evaluations**

Adverse effects in 7% (5 of 75 patients) were judged by the investigator to be probably or definitely drug related. The most common complaints included anxiety, insomnia, headache, nausea, and diarrhea. Most of the reported adverse events were judged to be mild in character by the investigators, and no patients discontinued therapy because of drug-related adverse events.

**DISCUSSION**

Levofloxacin was found to be highly effective against Legionella infections, leading to clinical success in >90% of patients. It should be noted that,
while not all patients with Legionnaires disease in these six studies fulfilled the criteria for cure, not a single patient died during the course of hospitalization and/or treatment. Levofoxacin treatment was as successful in patients with severe CAP as in those with mild-to-moderate disease. During the post-therapy visit, clinical success was seen in 93.6% of patients with mild-to-moderate pneumonia, compared with 91.6% with severe pneumonia, with no documented microbiologic relapse in either patient group.

For 13 patients with Legionella, a high-dose (750 mg), short-course (5 day) levofoxacin treatment was administered. This regimen was based on the rationale that higher concentration peaks lead to increased killing of the pathogen, decreased resistance development, and higher patient compliance with the shorter course. The 750-mg dose increases peak plasma concentration twofold over the 500-mg dose at steady state, while maintaining a high drug concentration in the alveolar macrophages (105.1 μg/mL 4 h after dosing).12 The clinical cure rate was 92.3% (12 of 13 patients) at posttherapy; 5 of the patients had severe pneumonia. Although definitive conclusions cannot be drawn from the limited number of patients in this study, a high-dose, short-course therapy warrants scrutiny as a treatment option for Legionella-induced CAP.

In a meta-analysis of 13 studies of CAP in which an oral antibiotic could be administered, the respiratory quinolones showed a modest therapeutic advantage compared with other alternative antibiotics (such as macrolides, β-lactams, and doxycycline)22; 100% (10 of 10 patients) of fluoroquinolone-treated patients with Legionella infection were cured as compared to 33% (4 of 12 patients) treated with a β-lactam agent. In another retrospective observational study15 of 33 patients with Legionnaires disease, patients treated with a fluoroquinolone had fewer complications, more rapid defervescence, and lower mortality than patients treated with erythromycin; the differences, however, were not statistically significant.

Legionella infections account for up to 16% of cases of CAP, and in numerous observational studies Legionella is among the top four microbial causes of hospitalization due to CAP.6,23 The classic risk factors for Legionnaires disease include cigarette smoking, chronic lung disease, and immunosuppression; the disease most frequently occurs in the elderly.6

Based on a large-scale study of CAP in Ohio, the Centers for Disease Control and Prevention (CDC) estimated that only 3% of sporadic cases of Legionnaires disease are correctly diagnosed.24 It is probable that detection bias occurs such that those patients with the classic risk factors are more likely to undergo Legionella laboratory testing.

However, the demographics of the patients with Legionella in this large study deviated from the typical patient profiles, especially with >70% of the subjects being <65 years of age. Although approximately half of the patients had a history of respiratory illness and more than a fourth had a history of smoking, we found that approximately 34% (24 of 71 patients) did not have either of these risk factors. In addition, 14 of these 24 patients were also <55 years of age, providing evidence that Legionnaires disease is not limited to elderly patients with chronic respiratory illness or a history of smoking. None of the patients were known to be receiving immunosuppressive therapy, which is another key risk factor for Legionnaires disease. Interestingly, in a retrospective review of Legionnaires disease in Allegheny County, PA, Squier et al25 also found that 28% of reported cases had none of the classic risk factors for Legionnaires disease. These findings suggest that testing for Legionnaires disease is warranted in patients with CAP with broader demographics than previously appreciated. These data also suggest the need for an agent with intracellular activity when treating CAP regardless of the presence or absence of the typical Legionella risk factors.

This is the largest antibiotic study of patients with Legionella-induced CAP ever published. Levofoxacin proved to be highly efficacious at both the 500-mg and 750-mg doses, and mortality was negligible. With greater routine use of Legionella culture on selective media, it is likely that undiagnosed cases may be uncovered. Moreover, other Legionella serogroups and species not diagnosable by serology and urinary antigen may be identified as the actual etiology of CAP.

References
8 Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneun-
25 Squier C, Lin YE, Stout JE. Waterborne pathogens: Legionella and other opportunistic pathogens. Presented at the American Society of Healthcare Engineers of the American Hospital Association, July 16 to 18, 2001; Tampa, FL; abstract 055905