

Antimicrobial Chemotherapy for Legionnaires Disease: Levofloxacin versus Macrolides

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Background. The community outbreak of legionnaires disease that occurred in Murcia, Spain, in July 2001—to our knowledge, the largest such outbreak ever reported—afforded an unusual opportunity to compare the clinical response of patients with *Legionella* pneumonia treated with levofloxacin with that of patients treated with macrolides and to determine the role of rifampicin combined with levofloxacin in treating severe legionellosis.

Methods. An observational, prospective, nonrandomized study was conducted involving 292 patients seen at our hospital (Hospital "J. M. Morales Meseguer"; Murcia, Spain) who received a diagnosis of *Legionella* pneumonia during the Murcia outbreak. To compare both antibiotic regimens (macrolides vs. levofloxacin), patients were stratified by the severity of pneumonia. Duration of fever, clinical outcome, complications, side effects, and length of hospital stay were recorded. To assess the potential effects of adjuvant therapy with rifampicin, 45 case patients treated with levofloxacin plus rifampicin were evaluated and compared with 45 control pairs who were treated with levofloxacin alone.

Results. With the exception of 2 patients who died, all patients were cured. There were no significant differences between treatment groups in clinical outcome for patients with mild-to-moderate pneumonia. Nevertheless, in patients with severe pneumonia, levofloxacin exerted superior activity; it was associated with fewer complications (3.4% of patients receiving levofloxacin experienced complications, compared with 27.2% of patients receiving macrolides; $P = .02$) and shorter mean hospital stays (5.5 vs. 11.3 days; $P = .04$). Addition of rifampicin to the treatment regimen for patients receiving levofloxacin for severe pneumonia provides no additional benefit.

Conclusions. Our findings strongly suggest that monotherapy with levofloxacin is a safe and effective treatment for legionnaires disease, including in patients with severe disease. In these patients, levofloxacin appears to be more effective than clarithromycin.

Legionnaires disease (LD) is an acute pneumonia caused by *Legionella* species, a rod-shaped, gram-negative bacillus that is ubiquitous in aquatic reservoirs. Twenty-eight years after it was first detected [1], large, focal outbreaks of LD continue to occur worldwide. Since the early 1990s, the treatment of choice has shifted from erythromycin to newer macrozolides or fluoroquinolones [2–13]. Nevertheless, clinical experience with these agents is still limited, and there are many

aspects of treatment with these agents that currently remain unknown. Such aspects include the optimal duration of therapy, the preferred route of administration, and the impact of combination therapy.

The community outbreak of LD that occurred in the city of Murcia, Spain, in 2001 [14] was, to our knowledge, the largest such outbreak ever reported, and it afforded an unusual opportunity to conduct an observational study of treatment outcomes that compared macrolide therapy with quinolone therapy. We also analyze the role of combination therapy with levofloxacin and rifampicin.

PATIENTS AND METHODS

Patients. In July 2001, an outbreak involving >800 suspected cases of *Legionella pneumophila* pneumonia occurred in Murcia, Spain; 449 of these cases were con-

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firmed. A contaminated cooling tower in the area was the most likely source of infection. Strains were identified as *L. pneumophila* serogroup 1 [14].

Most cases (397) were seen at our hospital, a 400-bed acute care public hospital that serves ~200,000 people in the city of Murcia. Despite the sudden nature of the outbreak (with most cases occurring in a span of <10 days) [14], at the end of the first day of the outbreak, an active surveillance system to detect patients with pneumonia was established. Medical personnel of all services involved were informed and were asked to send clinical samples obtained from patients with suspected cases and to collect prospective clinical data with use of a standardized case record form. The following information was recorded: age, sex, smoking and alcohol habits, comorbid illnesses (i.e., diabetes mellitus; chronic lung disease; preexisting cardiac, renal, neurological or liver disease; and immunosuppression), clinical signs and symptoms of pneumonia, results of laboratory investigation, radiological findings, treatment, and outcome. Patients were monitored until 12 weeks after the diagnosis of pneumonia. The admission decision was made by physicians in the emergency department of the hospital.

Prior ambulatory antimicrobial treatment was defined as administration of any antimicrobial drug during the evolution of the current case of pneumonia before admission to the hospital. Respiratory failure was considered to have occurred when the arterial partial pressure of oxygen level was <60 mm Hg or oxygen saturation on room air was <90%. Hyponatremia was considered to have occurred when the serum sodium level was <135 mmol/L. Anemia was defined as a hemoglobin level <12 mg/dL, renal dysfunction was defined as a serum creatinine level >1.2 mg/dL, and leukocytosis was defined as a WBC count >11,000 cells/mm³. Patients were considered to be immunocompromised if they were receiving cytotoxic chemotherapy or immunosuppressive therapy for any underlying disease.

To assess the severity of pneumonia, patients were stratified into 5 severity classes with use of the risk scale of mortality in community-acquired pneumonia, as described in Fine et al. [15]. Complications were defined as the development of renal failure, pleural effusion, or admission to an intensive care unit (ICU) for hemodynamic instability, respiratory failure, or mechanical ventilation during hospitalization. Renal failure was defined as a serum creatinine level ≥ 2 mg/dL at any time during hospitalization in a patient without known previous impairment of renal function or an increase in serum creatinine level of ≥ 2 mg/dL in patients with previous impairment of renal function. Deaths were defined as pneumonia related if pneumonia was designated as the underlying or immediate cause of death or was determined to have had a major contributing role in the cause of death [16].

Case definition. A confirmed case of LD was defined as

one in a patient who fulfilled the epidemiological criteria and who experienced symptoms compatible with pneumonia, who showed radiological signs of infiltration, and who showed laboratory evidence of infection with *L. pneumophila*. Laboratory evidence included isolation of *L. pneumophila* from a respiratory sample, a 4-fold increase in antibody titers to *L. pneumophila* in paired acute-phase and convalescent-phase serum samples, or detection of *L. pneumophila* antigen in urine samples [17].

Microbiological evaluation. The microbiological evaluation included evaluation of sputum samples (if available), blood cultures, serum samples (obtained at admission and 3–9 weeks thereafter), and urine samples. Other invasive procedures were performed according to clinical judgment. The presence of *L. pneumophila* serogroup 1 antigens in unconcentrated urine samples was investigated with use of the Biotest *Legionella* urinary antigen test ELA (Biotest AG) [18]. Paired serological studies were performed with the indirect immunofluorescence assay (Vircell SL) [19, 20]. Respiratory samples and blood cultures were processed according to standard methods [20].

Antimicrobial therapy. Antimicrobial treatment after admission to the hospital was given according to clinical judgment by the physicians in charge. All patients received first-line anti-*Legionella* agents. It should be considered that therapeutic options in hospitalized patients were limited by institutional antibiotic policies. Only levofloxacin was included in the hospital formulary as an expanded-spectrum fluoroquinolone; oral azithromycin was not included, and intravenous formulations of azithromycin were not available in Spain at the time of the study. For this reason, hospitalized patients received either clarithromycin or levofloxacin. Route of administration of levofloxacin was oral or intravenous; when the intravenous route was initially used, a switch to oral therapy was usually achieved on the second or third day of treatment. Outpatients were treated with either oral levofloxacin or macrolides (i.e., azithromycin or clarithromycin).

Prospective cohort study. To assess the potential effects of adjuvant therapy with rifampicin, 45 case patients who were treated with levofloxacin plus rifampicin were evaluated. Forty-five control pairs, matched for the Fine score and respiratory failure, were selected from among patients treated with levofloxacin alone.

Statistical analysis. Results are expressed as mean (95% CI). Statistical analysis was performed with the Winstat 3.0 statistical program (Winstat) and SPSS statistics software, version 10.0 (SPSS). Continuous variables were compared by means of the independent Student's *t* test, and categorical variables were compared by means of the χ^2 test. *P* values $\leq .05$ were considered to be statistically significant.

RESULTS

Study Population

In the July 2001 outbreak of LD that occurred in Murcia [14], 397 patients with suspected LD were seen at our hospital. All patients fulfilled the clinical and epidemiological criteria for LD. Laboratory evidence of *L. pneumophila* infection was found in 292 patients. All 292 patients with confirmed LD were included in this study. The 105 patients excluded from analysis had baseline and clinical characteristics (i.e., age, sex, comorbid diseases, and severity of pneumonia) identical to those of the patients who were included.

The diagnosis of *Legionella* pneumonia was made by serological criteria alone in 125 patients and by detection of urinary antigen alone in 25 patients. In 140 patients, the results of serological studies and urinary antigen tests were positive, and in 4 patients, sputum culture results were also positive. One patient had a positive urinary antigen test result and a positive sputum culture, and another patient had both a positive sputum culture and a positive serological test result.

Of the 292 patients with a confirmed diagnosis of LD, 223 were hospitalized, and 69 were treated as outpatients. The patients included 191 male and 101 female patients. Their mean age was 58.8 years. Underlying diseases were noted in 119 (40.7%) of the patients. The distribution of severity of disease in our study shows that 224 patients (76.7%) had mild-to-moderate disease (Fine score, I–III) and 68 (23.2%) had severe disease (Fine score, IV–V). Respiratory failure was present in 83 (34.2%) of the 242 patients that had an assessment of gas exchange.

In 13 patients, there were associated complications. Ten patients were admitted to the ICU, and mechanical ventilation was required in 9. Two patients (0.6%) died. One death occurred in an elderly man with multiple underlying medical conditions who died of pneumonia on day 5 of treatment (macrolides and levofloxacin plus rifampicin administered alternatively), and the second death occurred in a man who developed multiorgan failure after 3 days of treatment with levofloxacin. Three patients developed pleural effusion during treatment.

Antimicrobial Therapy

At hospital admission, 53 patients (18.1%) had received prior antibiotic treatment for a median (\pm SD) of 1.5 ± 0.1 days. The drugs administered were amoxicillin/clavulanic acid (in 23 [43%] of the patients), macrolides (in 8 [15%]), cephalosporins (in 9 [17%]), quinolones (in 7 [13%]), and amoxicillin (in 6 [12%]).

After hospital admission, 35 patients received oral azithromycin (mean total dosage, 4.5 g), 32 patients received clarithromycin (po for 24 patients and iv for 8; mean total dosage, 15.3 g), and 187 patients received levofloxacin (po for 59 patients and iv for 128; mean total dosage, 8.1 g). Rifampicin was

prescribed concomitantly to 45 of the patients who were treated with levofloxacin and to 2 of the patients who were treated with clarithromycin (600 mg per day for a median of 6 days). Combination treatment was commenced at hospital admission or within the first 24–48 h of hospitalization. There were 38 patients who were not evaluable for treatment analysis (patients who were treated with both macrolides and levofloxacin or who had modifications in the antibiotic treatment received during the evolution of disease).

Assessment of Treatment Outcome

Levofloxacin versus macrolides. Patients who had received adjuvant therapy with rifampicin were excluded from this analysis and will be analyzed separately. Overall, there were no significant differences in age, sex, and comorbid illnesses between both groups of treatment, but there was a trend toward a major severity of illness in levofloxacin-treated patients (20.2% had a Fine score ≥ 4 , compared with 16.9% in the macrolides group) and the presence of respiratory failure was significantly more frequent in this group of patients (27% in the levofloxacin group vs. 11.6% in the macrolides group; $P = .03$). For this reason, patients were stratified into 2 severity classes: mild-to-moderate pneumonia (Fine score, ≤ 3) and severe pneumonia (Fine score, ≥ 4). The demographic and clinical characteristics of patients with mild-to-moderate disease were similar in both treatment groups, with the exception of a major frequency of respiratory failure in the levofloxacin group (23% in the levofloxacin group vs. 3% in the macrolides group; $P = .008$). Patients with severe pneumonia had similar demographic and clinical characteristics in both groups.

Table 1 shows the clinical response, comparing macrolide therapy with quinolone therapy. With the exception of 1 patient treated with levofloxacin who died, all patients had a good clinical response. There were no significant differences between groups of treatment in patients with mild-to-moderate pneumonia. Nevertheless, patients with severe disease who were treated with macrolides (clarithromycin) were more likely to have complications, and the mean length of hospital stay was significantly higher (11.3 vs. 5.5 days).

The incidence of overall side effects was similar in both treatment groups. Adverse effects included gastrointestinal problems, such as nausea, vomiting, or diarrhea (in 7.6% of the macrolide group vs. 4.8% of the levofloxacin group); liver toxicity (drug induced), defined as an increase in both aspartate aminotransferase and alanine aminotransferase levels (in 3% of the macrolide group vs. 2% of the levofloxacin group); and phlebitis. Patients treated with intravenous clarithromycin had a significantly higher frequency of phlebitis than did patients treated with intravenous levofloxacin (50% vs. 1.8%; $P < .001$).

Role of adjuvant therapy with rifampicin. Forty-five patients treated with levofloxacin plus rifampicin were compared

Table 1. Comparison of the clinical outcome for patients with *Legionella* pneumonia treated with either levofloxacin or macrolides.

Variable	Fine score ≤3			Fine score ≥4			All patients					
	Macrolide (n = 54)	Lvfx (n = 114)	P	IR (95% CI)	Macrolide ^a (n = 11)	Lvfx (n = 29)	P	IR (95% CI)	Macrolide (n = 65)	Lvfx (n = 143)	P	IR (95% CI)
Duration of fever, mean days (95% CI)	4.7 (4.1–5.3)	4.5 (4.1–4.9)	.5	...	4.2 (2–6.4)	4.2 (3.2–5.2)	.9	...	4.6 (4–5.2)	4.4 (4–4.8)	.5	...
Experienced complications	0	0	3 (27.2)	1 (3.4)	.02	9 (0.8–79.3)	3 (4.6)	1 (0.6)	.08	7.6 (0.6–55.9)
Experienced cure	54 (100)	114 (100)	11 (100)	28 (96.5)	.5	1.0 (0.5–2.0)	65 (100)	142 (99.3)	.4	1.0 (0.7–1.3)
Experienced side effects	8 (14.8)	12 (10.5)	.4	1.4 (0.5–3.1)	2 (18)	3 (10.3)	.6	1.7 (0.2–7.5)	10 (15.3)	15 (10.4)	.3	1.4 (0.6–2.8)
Hospital stay, mean days (95% CI)	4.3 (3–5.6)	4 (3.7–4.3)	.6	...	11.3 (5.9–16.7)	5.5 (4.5–6.5)	.04	...	7.2 (4.6–9.8)	4.4 (4.1–4.7)	.03	...

NOTE. Data are no. (%) of patients, unless otherwise indicated. IR, incidence ratio. Lvfx, levofloxacin.

^a All patients were treated with clarithromycin.

Table 2. Clinical response of patients treated with either levofloxacin and rifampicin or levofloxacin alone.

Variable	Lvfx and rifampicin (n = 45)	Lvfx alone (n = 45)	P	IR (95% CI)
Duration of fever, mean days (95% CI)	5.7 (4.7–6.7)	4.3 (3.7–4.9)	.03	...
Experienced cure	45 (100)	44 (97.7)	.3	1.0 (0.67–1.54)
Experienced complications	6 (13.3)	0 (0)	.01	...
Experienced side effects	9 (20)	5 (11)	.2	1.8 (0.60–5.37)
Hospital stay, mean days (95% CI)	8.9 (6.9–10.9)	5.4 (6.7–6.1)	.002	...

NOTE. Data are no. (%) of patients, unless otherwise indicated. IR, incidence ratio; Lvfx, levofloxacin.

with 45 control subjects treated with levofloxacin alone (table 2). There were no differences in age, sex, or comorbid illness. The distribution of Fine scores in both groups was as follows: 25 patients had Fine score \leq III, 15 had a Fine score of IV, and 5 had a Fine score of V. Patients who received adjuvant therapy with rifampicin were significantly more likely to have a positive urinary antigen test result (78% vs. 54%; $P = .02$).

With the exception of 1 patient treated with levofloxacin alone who died, all patients were cured. The mean duration of fever was longer in the group of patients who received adjuvant therapy with rifampicin. Complications developed more frequently among patients who received adjuvant therapy with rifampicin, and the hospital stay was longer for these patients than it was for those who received levofloxacin alone (mean duration [95% CI], 8.9 [6.9–10.9] days vs. 5.4 [4.7–6.1] days; $P = .002$). Patients who were treated with adjuvant rifampicin did show a trend toward a higher frequency of side effects (20% vs. 11%). Liver toxicity was observed in 9% of patients who received adjuvant rifampicin, compared with 2% of patients who received levofloxacin alone. The frequency of gastrointestinal symptoms was similar in both groups (6.6% in the adjuvant rifampicin group vs. 4.4% in the levofloxacin group).

DISCUSSION

The collection of prospective data during the outbreak of LD that occurred in Murcia had led us to compare the clinical response of patients treated with levofloxacin with that of patients treated with macrolides and to evaluate the role of adjuvant treatment with rifampicin. New macrolides and fluoroquinolones are currently among the first-line therapies for *Legionella* infection [2–4, 8, 10, 11, 13, 21–24]. The lack of randomized trials of antibiotic treatment of this disease means that decisions about the use of these antimicrobial agents have to be made on the basis of the results of laboratory studies and uncontrolled clinical studies [7–13, 22, 23]. Laboratory studies indicate that fluoroquinolones and newer macrolides have greater activity and better intracellular penetration than erythromycin [2, 5, 6, 8, 25–27]. Among the macrolides, azithromycin has been reported to be superior to clarithromycin or

erythromycin [28–32]. Among the fluoroquinolones, levofloxacin and gemifloxacin appear to be the most active [2, 33].

Because of the rarity of well-documented cases of LD, it is unlikely that an adequate comparative clinical trial to assess the activity of different antibiotic regimens will ever be made [8]. The large number of patients included in our study and the stratification of patients by the severity of pneumonia have minimized the potential limitations of the study (i.e., the fact that it is observational and nonrandomized). Taking all of these considerations into account, we have observed that both regimens appear to be therapeutically equivalent in patients with mild-to-moderate pneumonia. Nevertheless, patients with severe cases of disease treated with levofloxacin had a shorter hospital stay and a decreased rate of complications, compared with patients treated with macrolides. It should be noted that all patients with severe pneumonia in this study received clarithromycin. Further studies are necessary to compare levofloxacin with intravenous azithromycin, which is now available.

Some authors recommend the use of rifampicin for combination therapy with macrolides or quinolones in cases of severe, unresponsive disease [2, 25, 34]. Reasons to add rifampicin include the benefit observed for combination therapy in the guinea pig model [34–36] and anecdotal clinical information [2, 37]. Nevertheless, there is no convincing evidence of its effectiveness, and combinations may risk additional toxicity and drug interactions [6, 8, 11, 38].

Our study shows that adding rifampicin to levofloxacin therapy provides no additional benefit. We observed that duration of fever, rate of complications, and length of hospital stay were significantly increased in patients who were treated with rifampicin. Therefore, we believe that this difference was not a treatment group effect but, rather, was a consequence of differences in the severity of illness among patients in each treatment group, despite the fact that both groups had similar prognostic scores. The decision by a physician to add rifampicin to the treatment regimen often relies on the recognition of a positive *Legionella* urinary antigen test result, on their subjective impression of a patient's clinical appearance (which is not always in accordance with prognostic scoring systems), or on the de-

velopment of complications (e.g., admission to the ICU) within the first 24–48 h. It is probable that, in some cases, none of these rules exactly define the severity of illness, and they would not supersede a physician's judgment [15, 39].

In summary, our findings strongly suggest that levofloxacin is a safe and effective treatment for *Legionella* pneumonia. Levofloxacin appears to be more effective than clarithromycin in treating severe cases of LD, but drawing the same conclusion about azithromycin may not be valid. Monotherapy with levofloxacin seems to be as effective as combination therapy with rifampicin.

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