

Antimicrobial Chemotherapy for Legionnaires' Disease: Levofloxacin Versus Macrolides



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Erythromycin has been the most commonly used drug for the treatment of Legionnaires' disease (LD). In recent years, however, some authors have proposed that therapy should consist of a fluoroquinolone or one of the newer macrolide-azalide antimicrobials rather than erythromycin. Nevertheless, clinical experience with these agents is still limited and there are many questions and aspects that remain currently unknown. Macrolides and quinolones have been compared *in vitro* and *in vivo*. As a class, fluoroquinolone antimicrobials have the greatest activity against *Legionella pneumophila* in experimental models. Clinical comparison of macrolides and quinolones are based in retrospective studies with a small number of patients and not usually controlled for severity of disease, often concentrating on severe hospitalized cases. The general picture to emerge from such studies is that quinolones are more active than macrolides.

We have taken advantage of a large community outbreak of LD, which occurred in Murcia, Spain, to perform an observational, prospective study of treatment outcomes, comparing macrolide therapy with quinolone (levofloxacin) therapy (1). The study included 292 patients with confirmed LD. Results from our study indicate that levofloxacin is highly effective and safe in the treatment of LD and appears to be superior to clarithromycin therapy for severe disease with respect to development of complications, reduction in the number of bed days, and side effects. In conclusion, levofloxacin offers a safe and effective alternative for the treatment of LD.

Introduction

Legionella pneumophila is an intracellular-growing Gram-negative microorganism and the causative agent of Legionnaires' disease (LD). Since LD was first identified in 1976 during an outbreak at an American Legion Convention in Philadelphia, outbreaks and sporadic cases of LD continue to occur worldwide (2). Pneumonia is the predominant clinical manifestation of *Legionella* infection. However, other presentations can occur.

LD is initiated by inhalation, and possibly microaspiration, of *Legionella* bacteria into the lungs. Once the bacteria enter the lung, they penetrate and proliferate within the phagosomes of alveolar macrophages and blood monocytes (3). The incubation period for LD ranges from 2 to 10 days.

Predisposing factors for LD include male sex, cigarette smoking, chronic heart or lung disease, diabetes, end-stage renal failure, organ

transplantation, immunosuppression, some forms of cancer, and age greater than 50 (4,5).

Illness usually starts with nonspecific prodrome, including high fever, myalgias, malaise, and headache. The onset of illness is often acute. Initially respiratory symptoms are not prominent; the cough usually is mild and nonproductive. Almost one third of patients have pleuritic chest pain. Gastrointestinal symptoms can be prominent in some patients. Many neurological symptoms have been described, but the most common are mental status changes, including confusion. The most common finding on chest radiographic examination is a patchy alveolar infiltrate involving a single lobe (4,5).

Since clinical and radiological manifestations of LD are nonspecific, definitive diagnosis requires application of specialized laboratory testing. Culture and urinary antigen are considered the

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most specific tests for diagnosis. The usefulness of urinary antigen detection for the diagnosis of LD has been well documented. Reported urinary antigen test sensitivities based on different studies, show overall sensitivities as high as 69–84% (6–12).

In our own institution we developed a study to evaluate urine antigen test sensitivity and a statistically significant association was found between clinical severity of pneumonia and test sensitivity; 85.7% for patients with severe pneumonia versus 37.9% for patients with mild pneumonia (13). Our results confirm the value of urinary antigen detection in providing a rapid diagnosis of *Legionella* pneumonia, especially in patients with severe illness. Nevertheless patients with mild pneumonia may go under-diagnosed, indicating that urinary antigen testing cannot replace other diagnostic methods. Therefore, where there is a clinical or epidemiological suspicion of *Legionella* pneumonia, treatment must include antibiotic coverage for *L. pneumophila*.

LD can cause high morbidity and mortality if it is not treated properly. Mortality rates are highly variable, ranging from less than 1% to as high as 50%, depending on the underlying health of the patient, the promptness of specific therapy, and whether the disease is sporadic, nosocomial, or part of a large outbreak (2,13,14,15).

Erythromycin was chosen as the treatment of choice for LD based on the clinical experience of the 1976 Philadelphia epidemic. In a retrospective review, patients treated with erythromycin or tetracycline had a 50% lower mortality rate compared with patients treated with β -lactams (2). Erythromycin effectiveness was attributed to its intracellular activity.

More recently, a number of new antimicrobial agents have been developed, but formally assessing their comparative efficacy in treatment has proven difficult. No prospective, blinded, randomized clinical trials of therapy have been undertaken for any antimicrobial agent for LD. Despite the absence of such studies, a well-founded choice for the antibiotic treatment of patients with a *Legionella* infection can be made using the evidence from *in vitro* and cell culture studies, as well as studies in animal models (guinea pigs).

Laboratory data and animal studies indicate that fluoroquinolones and newer macrolide-azalides have greater activity against *L. pneumophila* and better intracellular penetration than erythromycin (16–23). A number of small uncontrolled or underpowered prospective controlled studies of the treatment of LD have shown that a small number of patients with LD have responded adequately to erythromycin, tetracycline, azithromycin, dirithromycin, clarithromycin, telithromycin, pefloxacin,

ciprofloxacin, gatifloxacin, grepafloxacin, sparfloxacin, trovafloxacin, and levofloxacin (24–31). For these reasons, some authors propose that certain fluoroquinolones or one of the newer macrolides should be the drug of choice for the treatment of established legionellosis (16,32–36).

The Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) currently recommend doxycycline, azithromycin, and various fluoroquinolones for treating *Legionella* respiratory infections (37,38). The main reasons to prescribe newer agents are the frequency of adverse effects with erythromycin (ototoxicity, cardiac arrhythmias, hepatitis, gastrointestinal toxicity, and intravenous [IV] intolerance) (39) and the observation of occasional treatment failures in patients with immunosuppression or severe disease (25,40–42). The pharmacodynamic advantages (e.g. better bioavailability, better penetration into macrophages, longer half-life) of newer agents support once-daily oral therapy, which provides convenience, compliance, and safety advantages (29,32,34).

The role of levofloxacin

As a class, fluoroquinolones antimicrobials have the greatest activity against *L. pneumophila* in experimental models. *In vitro*, the newer quinolones are highly active against all *Legionella* spp. and seem better choices than older quinolones, with respect to minimum inhibitory concentrations (MICs), intracellular activity and post-antibiotic effects (16,17). To date, antimicrobial resistance to quinolones has not been a problem in clinical isolates of *L. pneumophila* (43,44). *In vivo*, there are numerous case reports and small series of patients with LD treated successfully with quinolones (ciprofloxacin, ofloxacin, pefloxacin, sparfloxacin, and levofloxacin) (24,26–28,30,31,36).

Among the quinolones, levofloxacin appears to be one of the most active and has a very well documented safety profile. Levofloxacin possesses excellent pharmacokinetic properties: it is rapidly absorbed, extensively distributed into tissue, and concentrations of the drug are typically higher in the tissue or body fluid than in plasma. Peak plasma concentrations (C_{max}) are achieved in less than two hours. With approximately 90% of the dose excreted in the urine, a half-life of six to seven hours, and a post-antibiotic effect of two to three hours, levofloxacin can be used as a very effective once-daily therapy, which offers convenience and increased compliance for patients (45).

Levofloxacin can be administered orally and intravenously, and bioavailability is close to 100% following oral (PO) intake. This makes levofloxacin particularly suitable for step-down

therapy where the patient is started on an IV regimen and subsequently switched to PO therapy when there is an improvement.

There is a low rate of adverse drug reactions to levofloxacin. The great benefit with levofloxacin is that it is one of the fluoroquinolones least likely to cause any cardiovascular, central nervous system effects or phototoxicity, and does not have any major drug–drug interactions, compared to some of the other fluoroquinolones or macrolides.

The community outbreak of LD that occurred in Murcia, Spain in 2001 (46) provided a unique opportunity to assess information about clinical, diagnostic, and treatment aspects of LD. We took advantage of this outbreak of LD to perform an observational study of treatment outcomes, comparing macrolide therapy with levofloxacin therapy (1).

Patients and methods

We conducted an observational, prospective, non-randomized study of 292 patients in our hospital who were diagnosed of *Legionella* pneumonia during the 2001 Murcia outbreak (1). All patients fulfilled the epidemiological criteria: symptoms compatible with pneumonia, radiological signs of infiltration, and laboratory evidence of infection with *L. pneumophila*. Laboratory evidence included isolation of *L. pneumophila* from a respiratory sample or a fourfold rise in antibody titers to *L. pneumophila* in paired (acute–convalescent phase) sera or detection of *L. pneumophila* antigen in urine samples (9).

Antimicrobial treatment after admission was given according to clinical judgment by the physician in charge. All patients received first-line antimicrobial agents for the treatment of *L. pneumophila*. Hospitalized patients received either clarithromycin or levofloxacin. Administration of levofloxacin was either PO or IV; when IV therapy was initiated, a switch to PO therapy was usually achieved on the second or third day of treatment. Outpatients were treated with either PO levofloxacin or macrolides (azithromycin or clarithromycin).

To compare the antibiotic regimens (macrolides vs. levofloxacin), patients were stratified by the severity of pneumonia using the risk of mortality in community-acquired pneumonia scale described by Fine et al (47). Measurements were duration of fever, clinical outcome, complications, side effects and hospital stay.

Study results

This study included 292 patients with confirmed LD; 223 were hospitalized and 69 were treated as outpatients. There were 191 males and 101 females, and the mean age was 58.8 years. Underlying dis-

eases were noted in 119 (40.7%) patients. The distribution of severity of disease in our study shows that 224 (76.7%) patients had mild to moderate disease (Fine class I–III) and 68 (23.2%) suffered a severe disease (Fine class IV–V). Respiratory failure was present in 83 of the 242 patients (34.2%) that had an assessment of gas exchange.

There were associated complications in 13 patients. Ten patients were admitted to the intensive care unit (ICU) and mechanical ventilation was required for 9 patients. Death occurred in 2 patients (0.6%). Pleural effusion during treatment developed in 3 patients.

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 levofloxacin was given to 187 patients (PO for 59 patients and IV for 128; mean total dosage = 8.1 g). Rifampicin was prescribed concomitantly to 45 of the levofloxacin-treated patients and two of the clarithromycin-treated patients (600 mg per day for a median of 6 days). Combination treatment was commenced at hospital admission or within the first 24–48 hours of hospitalization. There were 38 patients non-evaluable for treatment analysis (patients treated with both macrolides and levofloxacin, or modifications in the antibiotic treatment during the evolution).

Patients who had received adjuvant therapy with rifampicin were excluded from this analysis.

Levofloxacin versus macrolides

Table 1 shows the clinical response, comparing macrolide therapy with quinolone therapy. With the exception of one patient treated with levofloxacin who died, all patients had a good clinical response. There were no significant differences between treatment groups 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 significantly higher mean length of hospital stay (11.3 vs. 5.5 days). The incidence of overall side effects was similar in both treatment groups. Patients treated with clarithromycin IV had a significantly higher frequency of phlebitis than patients treated with levofloxacin IV (50% vs. 1.8%; $p < 0.001$)

Discussion

The available evidence, based on *in vitro* and *in vivo* studies results suggest that quinolones or newer macrolides could be the treatment of choice in the case of severe *Legionella* pneumonia.

Macrolides and quinolones have been compared *in vitro* and *in vivo*. *In vitro*, the rank order

Table 1. Clinical outcome of patients treated with levofloxacin vs. macrolides

	Fine ≤ 3 (n = 168)			Fine ≥ 4 (n = 40)			Total (n = 208)		
	Macrolide (n = 54)	Levofloxacin (n = 114)	p value IR (CI 95%)	Macrolide ^a (n = 11)	Levofloxacin (n = 29)	p value IR (CI 95%)	Macrolide (n = 65)	Levofloxacin (n = 143)	p value IR (CI 95%)
Duration of fever (mean days ± CI 95%)	4.7 ± 0.6	4.5 ± 0.4	0.5	4.2 ± 2.2	4.2 ± 1	0.9	4.6 ± 0.6	4.4 ± 0.4	0.5
Complications	0	0	–	3 (27.2%)	1 (3.4%)	0.02 9 (0.8–79.3)	3 (4.6%)	1 (0.6%)	0.08 7.6 (0.6–55.9)
Outcome (cured)	54 (100%)	114 (100%)	–	11 (100%)	28 (96.5%)	0.5 1.0 (0.5–2.0)	65 (100%)	142 (99.3%)	0.4 1.0 (0.7–1.3)
Side effects	8 (14.8%)	12 (10.5%)	0.4 1.4 (0.5–3.1)	2 (18%)	3 (10.3%)	0.6 1.7 (0.2–7.5)	10 (15.3%)	15 (10.4%)	0.3 1.4 (0.6–2.8)
Hospital stay (mean days ± CI 95%)	4.3 ± 1.3	4 ± 0.3	0.6	11.3 ± 5.4	5.5 ± 1.0	0.04	7.2 ± 2.6	4.4 ± 0.3	0.03

^a All patients were treated with clarithromycin.

Abbreviations: IR = incidence ratio, CI = confidence interval.

of intracellular activity against *L. pneumophila* serogroup 1 was quinolones, ketolides, then macrolides. Among the macrolides, azithromycin appears to be the most active (17,48). Clinical comparison of macrolides and quinolones are based on retrospective studies with a small number of patients and are not usually controlled for severity of disease, often concentrating on severe hospitalized cases. The general picture to emerge from these studies is that quinolones are more active than macrolides.

One retrospective study suggests that pefloxacin therapy may be superior to erythromycin therapy for very severe LD (28). Another retrospective study of LD with severe pneumonia showed that patients treated with a fluoroquinolone within 8 hours of admission to an ICU had significantly better outcomes than those treated later, or with other drugs, including erythromycin (49).

A study by Mykietiuik et al demonstrated that patients who received levofloxacin therapy for LD had faster defervescence and clinical stability compared to patients treated with macrolides, thus allowing shorter hospital stays (50).

The LD outbreak in Murcia, Spain gave us an opportunity to conduct an observational, prospective, non-randomized study of treatment outcomes with a large number of patients, comparing macrolide therapy with levofloxacin therapy. The number of cases to examine in such studies is usually a problem, but not in this one. The problem of equating the patients in regard to severity of disease, history of disease, and confounding health conditions was still a problem. We minimized this by using the categories of Fine et al (47) to group patients according to severity.

Results from our study indicate that levofloxacin is highly effective and safe in the treatment of LD. It appears to be superior to clarithromycin therapy for severe disease with respect to the development of complications, reduction in the number of hospital bed days, and side effects.

It is obvious that such a study cannot provide conclusive results. The question of optimal therapy for LD should be answered using appropriately designed, randomized trials. There is still a need for more prospective studies to determine the role of IV formulations of azithromycin, now available, for severely ill patients. The lack of an IV formulation has limited the use of azithromycin in this group of patients since parenteral therapy is recommended until an objective clinical response is seen, before switching to PO therapy. Levofloxacin is very useful in this regard. Levofloxacin therapy allows the patient to stabilize very quickly and be discharged on effective, once-daily PO therapy (51–54). This is certainly associated with reduced costs in terms of hospitalization.

Additional reasons to use levofloxacin are its low rate of drug interactions, compared to some of the other fluoroquinolones or macrolides, and low rate of adverse drug reactions. In our study there were relatively few adverse drug reactions associated with levofloxacin. Gastrointestinal problems, such as nausea, vomiting, or diarrhea were present in 4.8% of treated patients, liver toxicity in 2%, and phlebitis in 1.8% of patients treated with IV levofloxacin.

In conclusion, levofloxacin offers a safe and effective alternative for the treatment of LD including those patients with severe disease.

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