Fluoroquinolones vs Macrolides in the Treatment of Legionnaires Disease*

Miquel Sabrià, MD, PhD; María Luisa Pedro-Botet, MD, PhD; Joaquín Gómez, MD, PhD; Jorge Roig, MD, PhD; Blanca Vilaseca, MD; Nieves Sopena, MD, PhD; and Víctor Baños, MD, PhD; for the Legionnaires Disease Therapy Group†

**Background:** Erythromycin has been the treatment of choice for Legionnaires disease (LD). However, treatment failure and experimental evidence of its bacteriostatic effect have led to evaluation of new drugs such as fluoroquinolones. This study compared the evolution of patients with LD treated with macrolides and fluoroquinolones.

**Methods:** A prospective observational study was performed, and 130 patients from three centers were included. Diagnoses were made using Legionella urinary antigen assay in all patients. Patients receiving any antibiotic > 36 h before starting the study therapy were excluded. Group 1 included 76 patients who received macrolides (33 patients with erythromycin and 43 patients with clarithromycin), and group 2 included 54 patients treated with fluoroquinolones (50 patients with levofloxacin and 4 patients with ofloxacin).

**Results:** No significant differences were seen between the two groups regarding age, sex, smoking, alcohol intake, underlying diseases, or community/hospital acquisition. The time from onset of LD symptoms until the initiation of antibiotic treatment was 78.5 h and 92.7 h in groups 1 and 2, respectively (p = 0.1). Time to apyrexia was significantly longer in the macrolide group (77.1 h vs 48 h for groups 1 and 2, respectively; p = 0.000). There were no differences according to radiology, clinical complications, or mortality. Nevertheless, a trend to a longer hospital stay was observed in the macrolide group (9.9 days vs 7.6 days in groups 1 and 2, respectively; p = 0.09).

**Conclusions:** Fluoroquinolones were as effective as erythromycin in the treatment of LD. It is of note that time to apyrexia was significantly shorter and hospital stay tended to be shorter in patients receiving fluoroquinolones.

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**Key words:** fluoroquinolones; Legionella; Legionnaires disease; macrolides; pneumonia

**Abbreviations:** AUC = area under concentration 24-h time curve; LD = Legionnaires disease; MIC = minimum inhibitory concentration

Erythromycin has been the treatment of choice for Legionnaires disease (LD) since a retrospective study1 of the epidemic outbreak in Philadelphia in 1976 showed a significantly lower death rate in patients treated with this antibiotic. Nevertheless, reports of treatment failure with erythromycin, the interference of this antibiotic with the metabolism of numerous drugs, especially in immunosuppressed patients, as well as the appearance of secondary effects with the use of high doses have led to the evaluation of new antibiotics in the treatment of this infection.2–4 Despite good extracellular and intracellular activity,5,6 the effect of clarithromycin is still bacteriostatic against Legionella.7,8

Legionella is an intracellular pathogen, and antibiotics with adequate intracellular penetration are more likely to be efficacious. Fluoroquinolones achieve high intracellular levels and have a lower minimum inhibitory concentration (MIC) against Legionella than erythromycin.9,10 Moreover, experimental studies11–14 have demonstrated that these antibiotics irreversibly inhibit the multiplication of Legionella.
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Fluoroquinolones and macrolides have been indistinctly used in many hospitals as the standard treatment of LD. This study evaluated different variables related to the clinical evolution of Legionella infection in patients with LD treated with fluoroquinolones and macrolides.

Materials and Methods

The study was observational. Cases of LD from Hospital Universitario Germans Trias i Pujol, in Badalona, Spain (n = 53); Virgen de la Arrixaca Hospital, in Murcia, Spain (n = 68); and Nostra Senyora de Meritxell Hospital, in Escaldes, Principality of Andorra (n = 9) were included. Data from Virgen de Arrixaca Hospital were prospectively collected during the outbreak of LD in Murcia in 200217 and data from Hospital Universitario Germans Trias i Pujol and Nostra Senyora de Meritxell Hospitals were obtained from a Legionella database prospectively collected from 1995 until the present (from 2001 for Nostra Senyora de Meritxell Hospital). All the patients from this last hospital were exclusively treated with clarithromycin.

In order to exclude additional pathogens, blood culture and urinary Streptococcus pneumoniae antigen test results were negative in all the patients. Sputum cultures were performed in only a few patients because of the difficulty to obtain a good specimen and the retrospective nature of this study. Results of serologic tests in order to rule out Chlamydia psittaci, Chlamydia pneumoniae, Coxiella burnetti, and Mycoplasma pneumoniae infection were recorded from 50 patients (38.4%) and were negative in all.

Inclusion and Exclusion Criteria

Patients receiving either macrolides (erythromycin or clarithromycin) or fluoroquinolones (ofloxacin or levofloxacin) for definitive LD were included in the study. Doses considered appropriate for inclusion were as follows: 500 to 1,000 mg of erythromycin q6h, or 500 mg of clarithromycin q12h by the IV or oral route; ofloxacin at 400 mg or levofloxacin at 500 mg q12h IV until apyrexia, and thereafter 400 mg or 500 mg po qd. The treatment was > 14 days in all the cases. Patients who had received another antibiotic > 36 h before starting the study therapy and those who were treated at doses considered to be inadequate or over a treatment period of < 14 days were excluded from the study.

Selection Groups

One hundred thirty patients fulfilled the inclusion criteria and were classified into two groups. Diagnoses were made in all patients using Legionella pneumophila serogroup 1 urinary antigen assay. Group 1 included 76 patients who had received treatment with erythromycin (n = 33) or with clarithromycin (n = 43), and group 2 included 54 patients treated with fluoroquinolones (50 with levofloxacin and 4 with ofloxacin).

Group Characteristics

Demographic data and predisposing factors are shown in Table 1. No significant differences were observed between the two groups with respect to these variables.

Data Collected

A protocol for data collection including time to apyrexia, clinical evolution, mortality, and mean hospital stay was applied.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (Macrolides) [n = 76]</th>
<th>Group 2 (Fluoroquinolones) [n = 54]</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), yr</td>
<td>60 (23–84)</td>
<td>57.4 (21–87)</td>
<td>0.3</td>
</tr>
<tr>
<td>Male gender</td>
<td>62 (81.5)</td>
<td>36 (66.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Community-acquired LD</td>
<td>64 (84.2)</td>
<td>43 (79.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Interval (range), h†</td>
<td>78.5 (24–240)</td>
<td>92.7 (12–360)</td>
<td>0.1</td>
</tr>
<tr>
<td>Respiratory failure‡</td>
<td>39 (51.3)</td>
<td>31 (57.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>ICU admission‡</td>
<td>9 (11.8)</td>
<td>6 (11.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>No underlying disease</td>
<td>17 (22.3)</td>
<td>17 (31.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>38 (50)</td>
<td>29 (53.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>13 (17.1)</td>
<td>5 (9.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (32.8)</td>
<td>14 (25.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (14.4)</td>
<td>10 (18.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>17 (22.3)</td>
<td>17 (31.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>5 (6.5)</td>
<td>2 (3.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>5 (6.5)</td>
<td>3 (5.5)</td>
<td>1</td>
</tr>
<tr>
<td>Transplant recipient</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Solid neoplasm</td>
<td>14 (18.4)</td>
<td>4 (7.4)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hematologic neoplasm</td>
<td>3 (3.9)</td>
<td>4 (7.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>10 (13.1)</td>
<td>7 (12.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>HIV, No. of patients (mean CD4 cells/UL); %</td>
<td>2 (389); 2.6</td>
<td>4 (468); 7.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.
†Interval of time from the onset of symptoms to the initiation of antibiotic treatment.
‡At clinical presentation.
The Kolmogorov-Smirnov test and the Levene test were performed to assess population normality and the homogeneity of variances, respectively. Means were compared by the Student t test or the Mann-Whitney U test when appropriate. Proportions were compared using the χ² test with Yates correction or Fisher Exact Test when necessary. All p values and confidence intervals were two sided. All confidence interval estimates were 95%.

RESULTS

Comparative data on evolution are shown in Table 2. The mean time to apyrexia in group 1 was 77.1 h (range, 24 to 408 h), and 48 h (range, 24 to 192 h) in group 2 (p = 0.000). The breakdown on duration of IV vs oral therapy was 5.3 days for patients receiving macrolides and 9.9 days for those receiving fluoroquinolones (p = 0.000). The following complications were observed during the evolution of Legionella pneumonia: pleural effusion, empyema, mechanical ventilation, and septic shock. The global incidence of complications was greater in group 1 (23.6%) compared to group 2 (16.6%) (p = 0.4). Thirteen of 76 patients (17.1%) vs 5 of 54 patients (9.2%) (p = 0.2) presented pleural effusion in groups 1 and 2, respectively. Only one patient in group 1 and no patients in group 2 had pleural empyema. Mechanical ventilation was required in 5 of 76 patients (6.5%), compared to 3 of 54 patients (5.5%) (p = 1) in groups 1 and 2, respectively. In group 1, 6 of 76 patients (7.8%) presented with septic shock, compared to 3 of 54 patients (5.5%) (p = 0.7). Cavitation was not observed in either group. The mean length of hospitalization for Legionella pneumonia was 9.9 days in group 1 (range, 2 to 59 days) and 7.6 days in group 2 (range, 1 to 19 days) (p = 0.09). Finally, the mortality rates were 7.8% in group 1 and 5.5% in group 2 (p = 0.7).

DISCUSSION

Erythromycin has been the treatment of choice in LD for many years. The poor outcome reported in some clinical reports18–20 in patients with severe LD, especially in immunosuppressed patients, and the numerous side effects observed when using high doses of erythromycin have led to the consideration of new antimicrobial agents. To date, azithromycin, fluoroquinolones, and ketolides are among the most promising alternative antimicrobials to be considered according to experimental data and anecdotal clinical observations. Nevertheless, no comparative studies have been published on the treatment of LD. Furthermore, the relative rarity of LD until the availability of Legionella urinary antigen and its widely variable outcome make an adequate comparative clinical trial of the disease unlikely to be completed. Fluoroquinolones have shown the greatest activity against L pneumophila in experimental models. This group of drugs is very active against intracellular L pneumophila and is more effective than erythromycin in inhibiting the growth of L pneumophila in different intracellular models.21

Moreover, many fluoroquinolones kill, rather than just inhibit, intracellular bacterium replication.12,14,22 Ciprofloxacin, levofloxacin, sparfloxacin, and trovafloxacin were more active than erythromycin in guinea pig models of Legionella pneumonia and Legionella peritonitis.21 Ofloxacin and levofloxacin have been successfully used in the treatment of LD despite heavy immunosuppression in some of the patients treated.15,23,24

To our knowledge, this is the first study comparing macrolides vs fluoroquinolones in the treatment of LD. Assuming the low mortality rate of LD in the community or even in a hospital scenario, a comparative study to detect differences in this variable would probably need hundreds of patients in each study arm.25 However, to demonstrate differences in some aspects of clinical evolution, the size of the study arms does not necessarily need to be so large. Thus, time to apyrexia was found to be significantly shorter in the group of patients with LD treated with fluoroquinolones. Consequently, the switch from IV to oral therapy was achieved sooner in patients
receiving fluoroquinolones. In addition, a trend to a shorter hospital stay, as a consequence of the faster clinical improvement, was observed in patients treated with ofloxacin and levofloxacin.

It is important to point out that the starting doses of fluoroquinolones were double (500 mg twice) those of standard doses or doses recommended by the manufacturer (Sanofi-Aventis; Paris, France) in case of pneumonia (500 μg/24 h). In the experience of some of the authors, doses of 500 mg q24h do not seem to be as effective as the schedule recommended in this study. However, reports of treatment failure have been described using low doses of ofloxacin or ciprofloxacin in LD. Dosing every 12 h should lead the levofloxacin concentration to exceed the MIC for a longer period, improving the ratio of the area under concentration 24-h time curve (AUC) to the MIC (AUC/MIC ratio). For concentration-dependent drugs such as fluoroquinolones, the AUC/MIC ratio is the dynamic variable most clearly linked to the killing rate and outcome. The impact of these pharmacokinetics is reinforced by the experimental data showing a statistically significant decrease in colony forming units per milliliter with increasing concentrations of levofloxacin using a human monocye model against L pneumophila.

The reason for early improvement in the group treated with fluoroquinolones is unknown, although it is probably related to a more marked decrease in pulmonary bacterial load. Nonetheless, recovery of these patients is faster, and they may be discharged sooner. Even a reduction in hospital stay of only 24 h can greatly reduce health-care costs, thereby justifying a relatively more expensive treatment. Although not evaluated in this study, the rate of adverse effects is probably lower in patients receiving fluoroquinolones than in those receiving macrolides, as suggested by other authors.

However, complications and mortality rates were similar in both groups, which may be expected due to the reasons pointed out previously. However, complications and mortality rate in LD depend on the timing of the administration of appropriate antimicrobial therapy as well as other very important variables, such as the presence of immunosuppression, the severity of the underlying diseases, and the severity of the pneumonia.

The advantages of choosing macrolides or fluoroquinolones for LD in healthy patients or community-acquired pneumonia may only be those reported in this study: shorter time to apyrexia, and consequently a more rapid achievement of good health status. Nevertheless, in these patients, complications and mortality are probably not influenced by the choice of either type of drug. Thus, each physician should determine whether these advantages are sufficient to indicate treatment with one antibiotic or another.

To the contrary, in immunosuppressed patients or hospital-acquired LD, the experimental data, the anecdotal clinical observations, and the results of our study should be taken into account as a whole. A comparative study in this subgroup of patients with a worse clinical evolution and greater mortality would probably show significant differences in terms of mortality and complications that would favor the use of fluoroquinolones. The main weakness of this study is that it is not a randomized interventional trial. Nevertheless, we consider that the data available in the literature are, at present, sufficiently important to advise the use of fluoroquinolones when bad evolution of LD is suspected (immunosuppression, severe or hospital-acquired LD). Nonetheless, the present study is ongoing in the three hospitals participating in order to obtain a larger population sample for further information on the use of these two groups of antibiotics.

APPENDIX

Participating investigators are as follows: Miquel Sabrià, MD, PhD (Badalona, Spain); María Luisa Pedro-Botet, MD, PhD (Badalona, Spain); Joaquín Gómez, MD, PhD (Murcia, Spain); Jorge Roig, MD, PhD (Escaldes, Principality of Andorra); Blanca Vilaseca, MD (Badalona, Spain); Nieves Sopena, MD, PhD (Badalona, Spain); Victor Baños, MD, PhD (Murcia, Spain); Esteban Reynaga, MD (Badalona, Spain); Marian Gracia Núñez, Bsc (Badalona, Spain); Manuel Lorenzo, MD (Murcia, Spain); Javier Casal, MD (Escaldes, Principality of Andorra); Nicholas Ortega, MD (Murcia, Spain); Joaquín Ruiz, MD (Murcia, Spain) and Pere Tudela, MD (Badalona, Spain).

REFERENCES

7. Dubois J, St-Pierre C. In vitro activity, postantibiotic effect