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Randomized, Double-Blind Study of Prulifloxacin versus Ciprofloxacin in Patients with Acute Exacerbations of Chronic Bronchitis

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Key Words
Chronic bronchitis, acute exacerbation · Ciprofloxacin · Prulifloxacin · Fluoroquinolones

Abstract
Background: Recently the role of bacteria in acute exacerbations of chronic bronchitis (AECB) as well as antibiotic treatment with selected drugs, especially fluoroquinolones, have been better defined. ***Objective:*** To assess the efficacy and safety in patients with AECB of prulifloxacin in comparison with ciprofloxacin. ***Methods:*** AECB was defined according to the guidelines for the evaluation of new anti-infective drugs for the treatment of respiratory tract infections (1992). 235 patients took part in the trial; 117 (88 males and 29 females, mean age 64.8 years) received 600 mg prulifloxacin once daily and 118 (91 males and 27 females, mean age 64.5 years) 500 mg ciprofloxacin twice a day, for a duration of 10 days. The study design was randomized, multicenter, double-blind, double-dummy. Efficacy evaluations were performed by comparing pretreatment and posttreatment assessments. The clinical response was determined by 4-point rating scores on cough, dyspnea, and expectoration (volume and appearance). The microbiological response was assessed on sputum specimen. ***Results:*** Clinical success was observed in 84.7 and 85% of patients in the prulifloxacin and ciprofloxacin groups, respectively. The 95% confidence interval proved the equivalence of treatments. Both drugs successfully eradicated the most commonly isolated strains, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* Both treatments were well tolerated. Adverse drug reactions were always of mild or moderate intensity. ***Conclusion:*** The study showed that a 10-day course of prulifloxacin is as effective and safe as ciprofloxacin in the treatment of patients with AECB.

Introduction

Despite the controversy of the last years over the need to prescribe antibiotics in patients with acute exacerbations of chronic bronchitis (AECB), prospective randomized placebo-controlled trials showed a clear benefit for the use of antibiotics, particularly if patients have at least 2 of the following 3 symptoms: increased dyspnea, increased sputum volume, or increased sputum purulence. In this context, antibiotics are useful because they lead to a more rapid resolution of symptoms and a more rapid return of peak flow rate compared with placebo [1, 2]. In addition, antibiotics may prevent some patients from

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developing secondary pneumonia and may prolong the time between exacerbations.

Recently, a number of studies and one consensus statement have been reported that have increased the understanding of AECB and suggest approaches in selecting antimicrobial therapy [3–5]. Several new lines of evidence have emerged that have supported the role of bacteria in AECB using either new diagnostic modalities or research techniques. Bacterial pathogens can be isolated in significant concentrations from distal airways in about 50% of AECB and specific immune responses to surface-exposed antigens of the infecting pathogen have been shown to develop after an exacerbation [6].

Since their introduction in clinical practice fluoroquinolones have represented a valid alternative to the empiric treatment with other antibacterials due to the increasing incidence of microbial resistance. Bacterial AECB respond to antimicrobial therapy and quinolones have been demonstrated to be at least equivalent to coamoxiclav, second- and third-generation cephalosporins and other β-lactams [7].

Fluoroquinolones are presently considered as an acceptable therapeutic choice both in simple and complicated chronic bronchitis [4]. The new generation of approved quinolones, more potent against *Streptococcus pneumoniae* and anaerobes, did not appear to have an evident advantage in terms of clinical success rate in AECB, with respect to the previous generations [3]. Ciprofloxacin continues to be a standard reference in AECB and the first choice therapy when patients are at the risk for *Pseudomonas* infections [3, 5].

Prulifloxacin (AF3012 or NM441) is a new quinolonic antibacterial agent, prodrug of AF3013 (or NM394), extensively investigated in Europe and in Japan for the treatment of respiratory and urinary tract infections. In vitro studies have shown that prulifloxacin has a wide spectrum of antibacterial activity against gram-negative and gram-positive strains comparable to or higher than that of other reference drugs [8, 9].

After oral administration, prulifloxacin is absorbed through the intestinal tract and is transformed by a paroxonase into the active compound [10]. Prulifloxacin is then distributed to the tissues reaching mean tissue concentrations in human lungs up to 5 times higher than in plasma.

Multiple-dose studies with prulifloxacin 600 mg once daily have demonstrated steady state mean peak plasma concentrations of 1.99 μg/ml approximately 1 h after oral administration with an elimination half-life up to 10 h. The peak levels exceed prulifloxacin MIC_{90} in recent isolates of *Haemophilus influenzae* (0.015 μg/ml), *Klebsiella pneumoniae* (0.12 μg/ml) and *Moraxella catarrhalis* (0.06 μg/ml) [11]. Elevated lung concentrations and low MIC_{90} of prulifloxacin against the most frequent pathogens involved in exacerbations of chronic bronchitis render the drug a possible therapeutic tool in patients with AECB.

Based on the above considerations, the present study was performed to evaluate the efficacy and safety of a 10-day regimen of prulifloxacin 600 mg once daily as compared to ciprofloxacin 500 mg twice daily.

Patients and Methods

Patients

Adult patients aged 18–80 years with an acute episode of chronic bronchitis as defined by a cough productive of sputum for at least 3 consecutive months for more than 2 consecutive years were eligible. Patients had to present at least two of the following symptoms and signs: increased cough and/or dyspnea, increased sputum volume, or increased sputum purulence. A chest X-ray confirming the absence of pneumonia was also requested [12]. Patients were excluded from study participation because of known quinolone hypersensitivity, pregnancy and lactation, significant renal or hepatic impairment, concurrent infections or recent antibiotic therapy.

Study Design

This randomized, double-blind, double-dummy, ciprofloxacin-controlled clinical trial was performed in 18 French and 7 Italian centers. The study protocol was approved by their ethics committees and all patients gave written informed consent before participating in the study.

Patients were screened and randomized to receive prulifloxacin 600 mg once daily or ciprofloxacin 500 mg twice daily for 10 days. Patients were assessed at baseline (visit 1), on day 5–7 during treatment (visit 2), on day 10–12 (0–48 h posttreatment: visit 3) and at follow-up (2 weeks after the end of treatment: visit 4). At visit 1 demographic characteristics, physical examination and medical history were recorded. Before and after treatment biochemical and hematological analyses, urinalysis and sputum specimens were assessed. At the follow-up visit patients were reevaluated with a full clinical assessment and, when appropriate, with a microbiological examination.

Efficacy and Tolerability Parameters

The primary efficacy parameter was the clinical outcome. Patients were defined as cured (resolution of all baseline symptoms), improved (decrease in intensity of all symptoms) or failed (no decrease in the intensity of at least one symptom detected at baseline). Clinical cure or improvement was considered a therapeutic success [12].

The bronchopulmonary origin of sputum samples was verified by Bartlett's score [13], based on the number of neutrophils per field (10–25 = +1; >25 = +2), epithelial pavement cells per field (10–25 = –1; >25 = –2) and mucus (+1). A total score >0 was required to microbiologically evaluate patients.

Table 1. Characteristics of patients

	Prulifloxacin	Ciprofloxacin
Gender, %		
Male	75.2 (88)	77.1 (91)
Female	24.8 (29)	22.9 (27)
Age[a], years	67.0; 33–83 (117)	65.5; 34–80 (118)
Weight[b], kg	69.3 ± 13.3 (117)	68.5 ± 11.1 (118)
Systolic pressure[b], mm Hg	141 ± 15.5 (116)	141 ± 17.2 (117)
Diastolic pressure[b], mm Hg	77.6 ± 11.5 (116)	77.4 ± 11.2 (117)
Pulse rate[b], beats/min	76.8 ± 11.9 (116)	76.0 ± 11.1 (116)
FEV_1, %		
≥ 50% of predicted value	46.1 (54)	42.7 (50)
< 50% of predicted value	53.9 (63)	57.3 (67)

Number of patients is given in parentheses.
[a] Figures represent median and range.
[b] Figures represent mean ± SD.

The identification and susceptibility testing for isolated microorganisms in the sputum specimens were performed according to the National Committee for Clinical Laboratory Standards [14]. Susceptibility for prulifloxacin was defined as follows: susceptible (zone diameter >21 mm corresponding to MIC <1 μg/ml), and resistant (zone diameter <15 mm corresponding to MIC >4 μg/ml); all the strains showing a zone diameter of 16–20 mm were defined as moderately susceptible.

At the end of treatment, microbiological assessments were expressed as follows: eradication (the pathogen observed at baseline was not found at endpoint), presumed eradication (absence of sputum sample because the patient was clinically improved), persistence (the original pathogen was still observed at endpoint), and superinfection (a new pathogen was found at endpoint, regardless of whether the original pathogen was present).

Eradication and presumed eradication evaluated after the end of treatment were considered a microbiological success.

Statistical Analysis

The sample size was determined to demonstrate the equivalence of treatments by a noninferiority trial [15]. Assuming a clinical cure rate of 85% for ciprofloxacin, a prefixed producer's risk of 20%, a maximum difference between the test and control drug of 15% and a one-tailed confidence level of 95%, a sample size of at least 94 patients per treatment group was required [16].

Efficacy analysis was performed on the modified intention to treat (MITT) and the per protocol (PP) populations. MITT was defined as all randomized patients with basal and final evaluations; PP analysis was performed in patients with basal and final evaluations, treatment compliance ≥80% and not administered antibacterial concomitant treatments. Patients who withdrew for drug-related adverse events or lack of efficacy were considered failures.

To demonstrate the equivalence hypothesis the lower limit of the one-tailed 95% confidence interval for the difference between the efficacy rates should not exceed 15% [17]. All treated patients were included in the tolerability analysis.

Results

A total of 235 Caucasian patients entered the study; 117 received prulifloxacin 600 mg once daily and 118 ciprofloxacin 500 mg twice daily. Characteristics of the patients are summarized in table 1. Two hundred and twenty-one patients (94%) out of 235 patients completed the study, 14 patients (7 in each treatment group) were withdrawn from the study. The reasons for premature withdrawal (baseline resistant strains, adverse events, chronic liver or renal disease, pneumonia and lack of efficacy) were similarly distributed between the groups. At baseline clinical signs and symptoms occurred with similar frequency and severity in the two treatment groups. The percentage of patients on steroid therapy was 30.6% (34/111) and 29.2% (33/113) in the prulifloxacin and ciprofloxacin groups, respectively.

Clinical response was assessed in MITT and PP populations. The MITT population consisted of 224 patients (the 221 who completed the study plus 3 patients who were withdrawn for treatment-related adverse events or lack of efficacy). The PP population consisted of 222 patients (110 in the prulifloxacin group and 112 in the ciprofloxacin group): 1 was excluded for treatment compliance <80% (prulifloxacin group) and the other for antibacterial concomitant treatment (ciprofloxacin group).

Figure 1 shows the results in the MITT population at endpoint in terms of percentage of patients judged as cured, improved or failures. The 95% confidence interval confirmed the clinical equivalence of prulifloxacin and ciprofloxacin groups.

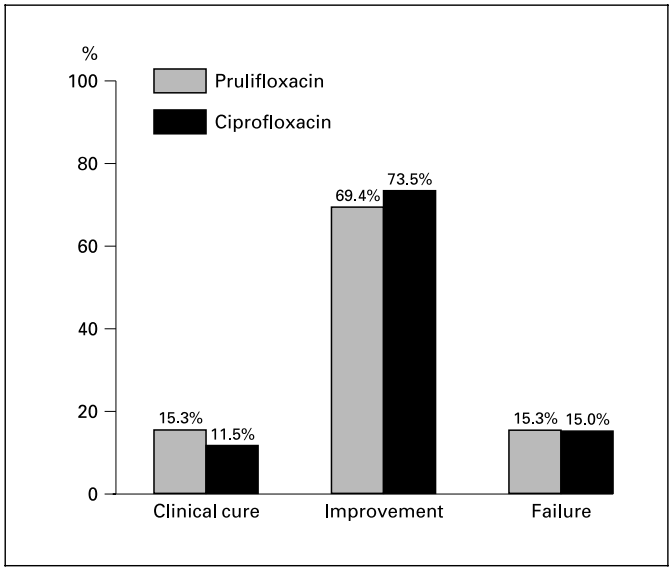

Fig. 1. Clinical efficacy at the end of treatment (MITT population).

Table 2. Clinical response rates at the end of treatment

	Prulifloxacin	Ciprofloxacin
MITT population		
Success/total patients	94/111	96/113
% (95% CI)	84.7 (78–91.4)	85 (78.4–91.5)
PP population		
Success/total patients	93/110	95/112
% (95% CI)	84.6 (77.8–91.3)	84.8 (78.2–91.5)

Table 3. Bacteriological response (eradication and presumed eradication) by pretreatment bacterial pathogens

	Prulifloxacin	Ciprofloxacin
Haemophilus influenzae	17/19 (89.5)	15/15 (100)
Streptococcus pneumoniae	8/9 (88.9)	9/12 (75)
Klebsiella pneumoniae	5/5 (100)	8/8 (100)
Pseudomonas aeruginosa	4/5 (80)	3/4 (75)
Staphylococcus aureus	5/5 (100)	2/2 (100)
Haemophilus parainfluenzae	2/2 (100)	1/1 (100)
Branhamella catarrhalis	1/1 (100)	2/2 (100)
Others	5/7 (71.4)	6/6 (100)
Total	47/53 (88.7)[a]	46/50 (92)[b]

Figures in parentheses represent percentage.
[a] 95% CI: 79.0–97.0%.
[b] 95% CI: 82.4–99.4%.

After 10 days' treatment, the clinical success rates in the MITT population were 84.7% for prulifloxacin and 85% for ciprofloxacin. Similar efficacy results were obtained in the PP population (table 2). The analysis performed in the subgroups of patients stratified according to the FEV_1 values at enrollment ($\geq$ or $<$ 50%) did not show statistically significant differences between groups and confirmed the equivalence of treatments. Clinical efficacy results between the groups were not modified by the stratification according to steroid coadministration.

One hundred and eighty-four patients (91 in the prulifloxacin group and 93 in the ciprofloxacin group) returned for the follow-up visit and were reevaluated in order to determine the frequency of relapses. Two out of 91 and 1 out of 93 patients presented exacerbations of chronic bronchitis when compared to visit 3.

One hundred and three causative bacterial strains were identified in the microbiologically evaluable population: 94 (50 in the prulifloxacin and 44 ciprofloxacin group) out of 221 patients (42.5%), defined as patients who completed the study, presented bacterial pathogen strains at baseline and were assessed at endpoint. The most common pathogens isolated were *H. influenzae* (30.6%), *S. pneumoniae* (18.9%), *K. pneumoniae* (11.7%) and *Pseudomonas aeruginosa* (8.1%). Six patients presented 6 resistant strains (4 resistant to both treatments and 2 resistant to ciprofloxacin and prulifloxacin, respectively). All but 1 patient did not drop out due to the concomitant partial resolution of the disease when the results of the antibiogram were provided.

The bacteriological success at endpoint for the primary pathogens isolated at pretreatment slightly varied across the treatment groups (table 3). The proportion of responses for *H. influenzae* was highest in the ciprofloxacin group, while the eradication rates of *S. pneumoniae* and *P. aeruginosa* were superior in the prulifloxacin group.

At endpoint, 4 clinically cured patients presenting eradication of the causative pathogen showed superinfection (2 in the prulifloxacin and 2 in the ciprofloxacin groups). The pathogens detected were *P. aeruginosa* (2 isolates), *Klebsiella oxytoca* and *Staphylococcus aureus*. Clinical resolution of the exacerbation of chronic bronchitis and the concomitant presence of pathogens is often reported [18, 19] and could be explained as being due to a further asymptomatic colonization of the lower airways.

At visit 4, microbiological assessments were performed only when appropriate (clinical deterioration of the patient's general condition): two persistences (*S. pneumoniae* and *Pseudomonas* spp. in the ciprofloxacin and prulifloxacin group, respectively) were detected. One or more

Table 4. Incidence of patients with adverse events (most commonly reported drug-related adverse events)

	Prulifloxacin (n = 117)	Ciprofloxacin (n = 118)
Diarrhea	2 (1.7)	1 (0.8)
Dyspepsia	2 (1.7)	1 (0.8)
Gastric pain	10 (8.5)	8 (6.8)
Gastrointestinal disturbance	0	2 (1.7)
Headache	0	1 (0.8)
Nausea	2 (1.7)	0
Pruritus	3 (2.5)	0
Vomiting	0	2 (1.7)

Figures in parentheses represent percentage.

drug-related, treatment-emergent adverse events were reported by 15.4% of patients (18/117) with prulifloxacin and by 12.7% of patients (15/118) in the ciprofloxacin group. The most common treatment-related adverse event was gastric pain of mild or moderate intensity reported in 8.5% (10/117) of the prulifloxacin patients and 6.8% (8/118) of the ciprofloxacin patients (table 4).

On the whole, both treatments were well tolerated. Only 2 patients dropped out for treatment-related adverse events: 1 patient (prulifloxacin group) for mild pruritus and moderate gastric pain, and 1 patient (ciprofloxacin group) for moderate fever, diarrhea and vomiting. During the study period a total of 8 (4 in each treatment group) non-treatment-related serious adverse events occurred: 5 out of 8 were assessed as being due to the disease under treatment and the remaining 3 events to concomitant diseases. All these events were defined as serious because they required hospitalization or its prolongation. The four serious adverse events in the prulifloxacin group were diagnosed as bronchopneumonial foci, a preexistent epidermoid lung cancer, angina pectoris, and cardiorespiratory insufficiency which resulted in the death of the patient. The death was attributed to the underlying disease. Two out of the 4 patients with serious adverse events in the ciprofloxacin group were diagnosed with nosocomial pneumonia (which required prolonged hospitalization) and pneumonia, respectively, and the remaining 2 patients presented respiratory insufficiency. No clinically significant differences in vital signs from baseline or consistent changes in clinically relevant hematology or chemistry were observed.

Discussion

The results of this double-blind study proved that prulifloxacin, a novel fluoroquinolone, is therapeutically equivalent to ciprofloxacin in patients with AECB, both in terms of efficacy and safety. After treatment, the clinical success rate was about 85% in both the prulifloxacin and ciprofloxacin treatment groups. The equivalence of the treatments was confirmed by the statistical analysis performed on the PP and MITT populations.

In this study only 94 patients (42.5%) presented at the enrollment one or more strains generally recognized as causing of AECB, due to the known critical problem of identifying pathogens in lower respiratory tract infections [12].

Eradication rates of causative bacteria were almost overlapping in the two study drugs. Although fluoroquinolones are generally not considered the first choice treatment of infections caused by *S. pneumoniae*, data emerging from this clinical trial evidenced a satisfactory microbiological efficacy of prulifloxacin against *S. pneumoniae*, slightly superior to the results obtained with the reference medication (table 3). An interesting result was also observed against *P. aeruginosa*. However, the small sample of strains detected during the study does not allow any definite conclusions to be made.

The impact of antibiotic selection, antimicrobial efficacy and related cost in AECB have recently been investigated [20]. Although pharmacy costs were lowest with first-line agents (amoxycillin, co-trimoxazole, tetracyclines, erythromycin), the use of third-line antimicrobials (co-amoxiclav, azithromycin, ciprofloxacin) significantly reduced the failure rate and need for hospitalization, prolonged the time between AECB episodes, and showed a lower total cost for the management of AECB. These data clearly indicate the role of ciprofloxacin as well as co-amoxiclav and azithromycin in the treatment of AECB, especially if they are considered from a pharmacoeconomic point of view. In this context, considering the equivalence with ciprofloxacin, prulifloxacin should represent a valid therapeutic alternative in the treatment of AECB.

The efficacy of treatment is influenced by several variables, such as the antibacterial broad spectrum, patient compliance, the individual absorption rate and, overall, the penetration of the drug into the target tissues. The significant activity against the most common pathogens isolated in patients with AECB, the good penetration into lung tissues and the long elimination half-life of prulifloxacin are probably fundamental to the results observed.

Good penetration in the site of infection as well as the easy administration are two characteristics of the ideal antibiotic for the treatment of AECB. In a recent survey, patient compliance was shown to be significantly improved when medications were given once or twice daily, rather than 3 or more times [3]. The once daily administration of prulifloxacin, which supports a better patient compliance, could be a key factor in the successful treatment of chronically ill patients.

In this study prulifloxacin showed a safety profile comparable to the reference medication and similar or better than that reported for other fluoroquinolones [21]. The majority of events observed were mild to moderate in severity. Biological monitoring did not show any clinically relevant variations. On the whole, the results of the trial proved the good efficacy and safety profile of prulifloxacin and its therapeutic equivalence with ciprofloxacin. However, it is evident that further studies are necessary to better define the potential role of prulifloxacin in the therapy of patients with AECB.

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