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Prulifloxacin vs Levofloxacin for Exacerbation of COPD after Failure of Other Antibiotics

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ABSTRACT

The chronic course and evolution of chronic obstructive pulmonary disease (COPD) is often characterized by periods of exacerbation of symptoms, which have a negative impact on the quality of life of patients, as well as on the evolution of COPD, and represent a significant cause of medical intervention and hospitalization. Very few data are available on the efficacy of rescue antibiotics in patients with acute exacerbation of COPD (AECOPD) unresponsive to previous treatment. The aim of this study was to evaluate the efficacy of two fluoroquinolones in AECOPD previously treated without success. The FADOI-FLOR study is a randomized, single-blind, non-inferiority comparison between levofloxacin and prulifloxacin. Primary endpoint was "therapeutic success" at Day 10 of treatment, defined as disappearance of signs/symptoms or decrease of at least three points of a global score of symptomatology (maximum score = 15). 258 patients were enrolled (128 levofloxacin and 130 prulifloxacin), in 25 centers. A very high proportion of patients in the two groups had therapeutic success at Day-10 (levofloxacin 93.0% vs prulifloxacin 96.7%, population intention-to-treat; 94.6% vs 99.1%, population per-protocol). Earlier therapeutic success (within 7 days) was achieved in 32.0% and 36.2% of patients receiving levofloxacin or prulifloxacin, respectively. At 3-month follow-up, re-exacerbations occurred in 17.8% of patients treated with levofloxacin and 14.2% of those receiving prulifloxacin ($p = 0.44$). In conclusion, fluoroquinolones are very effective in the treatment of AECOPD resistant to other antibiotics.

KEYWORDS

Exacerbation of COPD; hospitalization; levofloxacin; prulifloxacin; second-line antibiotic

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases in Western countries, with consequent high health and social impact (1–3). The chronic course and evolution of the disease are often characterized by periods of exacerbation of symptoms. They have a negative impact on the quality of life of patients (4, 5), as well as on the evolution of COPD (6, 7), and represent the most frequent cause of medical intervention and hospitalization in COPD patients. Around 50–70% of exacerbations are of infectious etiology; when bacterial infection is suspected, antibiotic treatment is suggested (8, 9). Failure of the ambulatory antibiotic treatment of acute re-exacerbation of COPD is not negligible (from 12 to 26%) (10, 11) and it is not uncommon that in these patients hospitalization occurs, due to persistent bad clinical conditions.

A study with the aim to evaluate a second-line antibiotic therapy in a population with these characteristics is of particular interest because of the potential therapeutic significance and originality of the experience. Fluoroquinolones have long been shown to be effective in the managementa of exacerbations because of their good pharmacological profile and high antimicrobial activity, particularly against Gram-negative pathogens (12). However, few specific data are available in the literature on the efficacy of fluoroquinolones in patients previously treated unsuccessfully with other types of drugs and admitted to hospital. In this perspective, it can be useful in assessment of the efficacy and tolerability of two different fluoroquinolones, levofloxacin and the more recent prulifloxacin (13), to evaluate a potential role of both, as well as possible peculiarities of the two molecules for the management of this selected patient population.

Patients and methods

Study design

FADOI-FLOR (ClinicalTrials.gov Identifier: NCT01710488) is a randomized, controlled, parallel-group, single-blind clinical trial, with a comparison between levofloxacin and prulifloxacin in patients with COPD exacerbation unresponsive to a different

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antibiotic therapy and hospitalized in internal medicine department. Patients were enrolled according to the following criteria:

- presence of purulent sputum documented by colorimetric test (14), plus at least two of the following signs/symptoms of at least 3-day duration: increased cough, increased dyspnea, and increase in sputum volume
- previous antibiotic treatment with any drug (e.g., amoxicillin, amoxicillin/clavulanic acid, cephalosporin, or macrolide) with the exclusion of fluoroquinolones, conducted for at least 3 full days with persistence or worsening of symptoms and consequent hospitalization
- age ≥ 60 years
- FEV_1 ≤80% and ≥30% and ratio FEV_1/FVC ≤0.7
- chest x-ray negative for inflammatory infiltrates
- informed consent

The list of exclusion criteria included diagnosis of asthma, pulmonary neoplasm, sepsis, tuberculosis, and cystic fibrosis; renal insufficiency or hepatic dysfunction; history of epilepsy, seizures, stroke (in the previous 6 months), or tendinopathy; known deficiencies for the glucose-6-phosphate dehydrogenase activity; drug addiction or alcohol abuse; and hypersensitivity or allergy to fluoroquinolones.

Outcome measures

Five signs/symptoms of COPD exacerbation were evaluated at baseline and along the period of experimental study treatment. A clinical score was calculated according to the following previously described semi-quantitative scale (maximum value of 15 points, corresponding to the worst clinical condition): (14–16)

- sputum purulence based on the colorimetric method described by Allegra et al. (14): score 0 = mucoid (white to gray); score 1 = mucopurulent (yellow); score 2 = purulent (green); score 3 = severe grade of purulence (brown)
- sputum volume evaluated within the first hour after awakening and classified as 0 = absent; 1 = mild (up to 1 teaspoon); 2 = moderate (1–2 teaspoons); 3 = severe (more than 2 teaspoons)
- dyspnea was scored as 0 = absent; 1 = mild (shortness of breath when hurrying on the level or up a slight hill); 2 = moderate (stops for breath when walking at own pace on the level); 3 = severe (stops for breath after walking about 150 meters or after a few minutes on the level)
- cough: 0 = absent; 1 = mild (only in the morning); 2 = moderate (reported night and day, but not disturbing sleep); 3 = severe (disturbing sleep)
  - fever: 0 = 37.0°C; 1 = > 37.0° and ≤ 37.5°; 2 = > 37.5° and ≤ 38.0°; 3 = > 38.0°

The primary study end-point was the percentage of patients with "therapeutic success" (disappearance of all signs/symptoms of disease or reduction of at least 3 points of the total score of symptomatology from baseline) at the conclusion of the cycle of antibiotic therapy (day 10), in the two study groups (levofloxacin and prulifloxacin).

Additional objectives of the study were percentage of "therapeutic success" (disappearance of all signs/symptoms of disease) at day 7, in the two study groups; evolution of C-reactive protein; episodes of exacerbation during the follow-up; safety of the treatments; and survival.

Study procedures

For each patient, the following information was scheduled to be collected for the purposes of the study. At Day 1 (baseline): demography and general characteristics (age, gender, height, weight, smoking habit), medical history and current diseases together with medications, previous antibiotic treatment for the index episode of COPD re-exacerbation, vital signs, lung function test, EKG, chest X-ray, hemoglobin saturation, blood gas analysis (in case of hemoglobin saturation less than 90%), sputum sample and culture (when possible), blood sample for routine hematology and serum chemistry, and signs/symptoms of COPD (study score). At Days 3-5-7-10: vital signs, medications, hemoglobin saturation and blood gas analysis, lung function, routine hematology and serum chemistry exams, assessment of the study score for symptomatology, and safety of the treatments. Possible occurrence of adverse drug reactions was also assessed at follow-up after 1 month, together with lung function test and number of COPD re-exacerbations. This latter and survival were recorded at the time of follow-up after 3-6-12 months. A specifically developed case report form in electronic format (e-CRF) was used for data collection.

The two study treatments (levofloxacin 500 mg orally once daily and prulifloxacin 600 mg orally once daily) were used according to a pre-defined randomization list, in blocks of 4 patients. The prescribing and dispensing of the drug was made by medical personnel not directly involved in the data collection and procedures for the study; therefore, the medical investigator and the nursing staff were not informed on the type of treatment carried out for each individual patient. The drugs were administered in the morning, about two hours before or after food intake. If after 3 full days of therapy no improvement of symptoms, or a clinical deterioration, occurred, the experimental treatment had to be interrupted and the patient assigned to different treatment.

The scheduled duration of antibiotic treatment was 10 days; early interruption at 7 days was planned in case of disappearance of all symptoms and signs. This treatment schedule is consistent with the drug label of levofloxacin and prulifloxacin, which indicates a treatment of 7–10 days for exacerbations of COPD and a maximum period of therapy of 10 days but with 2–3 days of additional treatment after disappearance of symptomatology, respectively.

The research was conducted in accordance with the existing rules and subject to approval by the Ethics Committees of the participating centers; signed informed consent was collected from each patient. The study was promoted by the FADOI Foundation Research Department, which provided the scientific and operational coordination. FADOI is the Italian Scientific Society of Hospital Internal Medicine.

Statistical aspects

The calculation of the sample size for the study was made by assuming non-inferiority of treatment with prulifloxacin compared to levofloxacin, in terms of percentage of patients with "therapeutic success" at the conclusion of the therapy cycle. Based on the hypothesis that a successful treatment with levofloxacin was likely to occur in around 75% of patients,

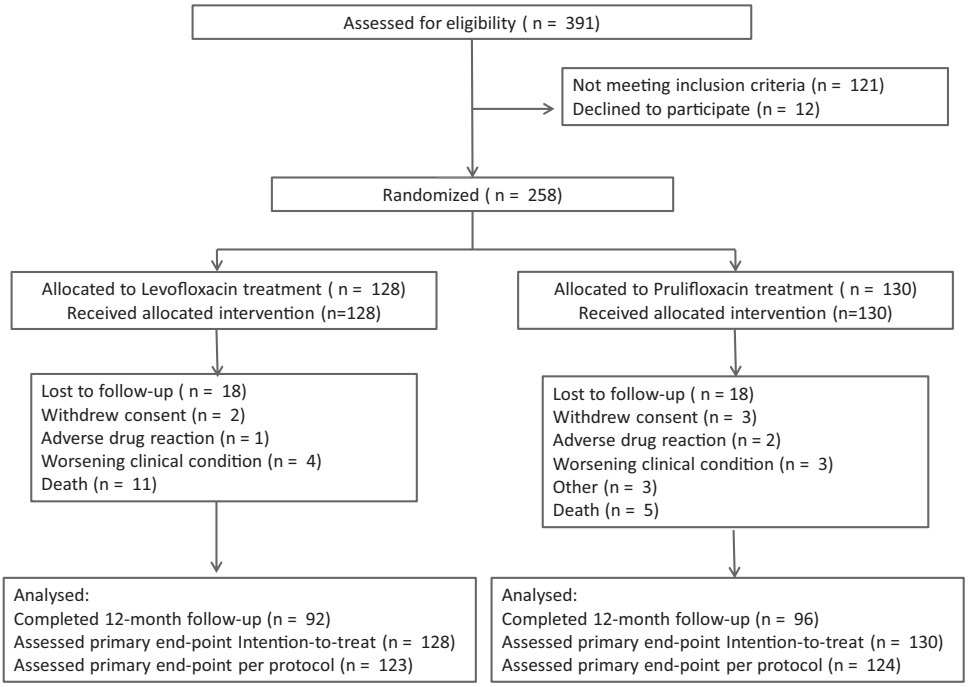

Figure 1. Flow diagram of patients' dispositions through study phases.

and assuming a limit of non-inferiority of 15%, 80% power of the test, and type I error equal to 0.025 (one-tailed test), a sample size of 132 valid patients for each treatment group was calculated.

The common descriptive statistics (mean, standard deviation, and minimum and maximum values for continuous variables; and absolute and relative frequencies for categorical variables) were calculated and stratified according to type of treatment. Statistical comparisons were made using one-way Analysis of Variance (ANOVA) (*t*-test) models when continuous variables were analyzed, and by applying Chi-square test (or Fisher's exact test, when appropriate) when categorical variables were taken into account. The analyses concerning the primary study end-point were carried out both on the "intention-to-treat" and "per-protocol" (patients with final assessment of treatment efficacy and compliance ≥ 80%) populations. The assessment of tolerability was relevant to the "safety" population (including all randomized patients who began the experimental treatment) and based on both laboratory parameters and clinically relevant adverse events. All statistical calculations were performed using SAS software version 9.1.3.

Results

A total of 258 patients have been enrolled in the study (182 males and 76 females), in 25 centers of internal medicine uniformly distributed in Italy.

Of the 258 patients enrolled, 128 have been treated with levofloxacin and 130 with prulifloxacin. The flow diagram of patients' disposition through study phases is reported in Figure 1. The percentage of patients who completed the 1-year follow-up is slightly greater in the prulifloxacin group compared to levofloxacin (76.9% vs 73.4%). For the purposes of the primary study end-point, 258 and 247 patients were included in the intention-to-treat and per-protocol populations (levofloxacin 128 and prulifloxacin 130; levofloxacin 123 and prulifloxacin 124, respectively).

Characteristics of the patient population at admission are described in Table 1. The results of the treatment groups are comparable. A high rate of co-morbidities was recorded—68.7% of patients had at least 2 acute or chronic diseases associated with the primary diagnosis of COPD. Charlson Index was 2.2±1.8 in the levofloxacin and 2.5 ± 2.2 in the prulifloxacin group, respectively. More than half of the enrolled patients (59.8% and 54.1% in the levofloxacin and prulifloxacin group) had more than 5 active pharmacological treatments at the time of randomization. As for the specific treatment for COPD (apart from antibiotics) at the time of admission to hospital, the majority of patients received a combination of bronchodilator and corticosteroid (systemic or inhaled), without significant differences between the study groups (Table 2). Corticosteroids alone were used in 5,8% and 6,2% of patients randomized to levofloxacin and prulifloxacin, respectively; 7.6% and 7.2% of patients treated with levofloxacin or prulifloxacin were receiving bronchodilator(s) without concomitant corticosteroids. The types of antibiotic used prior to hospitalization and without clinical response are listed inTable 3.

Few patients had a positive sputum culture, 11 and 8 in the levofloxacin and prulifloxacin group, respectively. *Pseudomonas aeruginosa* was the most frequently detected bacterium (4 and 2 cases).

At baseline, the symptoms evaluation scores were similar in the two study groups (Table 1, total score 7.3 ± 3.5 and 7.6 ± 3.5 for levofloxacin and prulifloxacin, p = NS). The 10-day treatment schedule was completed in 66.4% of patients, while 28.9% interrupted treatment at day 7 (therapeutic success reached) and 4.7% had duration of treatment less than 7 days in the levofloxacin group. The corresponding figures for prulifloxacin were 60.8%, 33.8%, and 5.4%. The evolution of the

Table 1. General characteristics of the patients at baseline. Values are expressed in percentages, unless otherwise stated.

Characteristics	Levofloxacin ($n = 128$)	Prulifloxacin ($n = 130$)	p value
Male gender	71.1	70.0	0.85
Age (years, mean ± SD)	76.5 ± 7.6	75.1 ± 7.5	0.14
Body mass index (mean ± SD)	27.7 ± 5.1	27.9 ± 5.3	0.91
Active smokers	28.1	32.3	0.46
Blood pressure (mmHg, mean ± SD)			
Systolic	132.2 ± 16.8	133.4 ± 14.1	0.52
Diastolic	76.5 ± 8.6	78.3 ± 8.5	0.09
Heart rate (per minute, mean ± SD)	82.7 ± 13.0	85.2 ± 12.2	0.11
Respiratory rate (per minute, mean ± SD)	21.5 ± 5.7	22.5 ± 5.9	0.16
FEV_1	43.7 ± 7.9	43.2 ± 9.2	0.91
Co-morbidities			
Cardiovascular diseases	43.8	38.5	0.44
Diseases of the digestive tract	11.7	13.1	0.85
Endocrine/metabolic diseases	8.6	6.2	0.48
C-reactive protein (mg/L)	8.2 ± 2.7	8.9 ± 3.1	0.05
Symptomatology			
Fever			0.17
≤ 37°C	69.5	68.2	
37.1–37.5°C	23.4	19.4	
37.6–38.0°C	6.3	7.0	
> 38.0°C	0.8	5.4	
Dyspnea			0.76
No	4.7	3.9	
Mild	25.8	27.9	
Moderate	48.4	51.9	
Severe	21.1	16.3	
Cough			0.55
No	0.8	2.3	
Mild	46.1	46.5	
Moderate	35.2	29.5	
Severe	18.0	21.7	
Sputum volume			0.90
Mild	38.3	39.6	
Moderate	41.4	38.8	
Severe	20.3	21.7	
Sputum appearance			
Mucopurulence	51.6	52.3	0.17
Purulence	35.7	28.1	
Severe grade of purulence	12.7	19.5	

total score in the two study groups, along the period of antibiotic treatment, was similar (Figure 2).

C-reactive protein levels decreased in a similar manner in the study groups (8.2 and 8.9 at Day 1 vs 2.9 and 4.0 mg/L at Day 10 in patients receiving levofloxacin and prulifloxacin, respectively, p = NS).

As reported in Table 4, more than 90% of patients had a therapeutic success at the end of treatment cycle in both study groups

Table 2. Treatment for COPD at the time of hospital admission (apart from antibiotics). Values are expressed in percentage.

Drugs	Levofloxacin ($n = 128$)	Prulifloxacin ($n = 130$)	p value
Corticosteroids	92.4	92.6	1.00
Systemic	29.5	39.5	0.12
Inhaled	16.7	8.7	0.06
Both	46.2	44.4	0.90
Bronchodilators	93.5	87.5	0.13
1, without corticosteroid	7.7	2.4	0.05
≥ 2, without corticosteroid	0	4.9	0.03
1, + corticosteroid(s)	38.4	34.5	0.60
≥ 2, + corticosteroid(s)	47.4	45.7	0.80

Table 3. Pharmacological classes of antibiotics used without clinical response prior to randomization. Values are expressed as percentages.

Drugs	Levofloxacin ($n = 128$)	Prulifloxacin ($n = 130$)	p value
Beta-lactams	10.1	13.1	0.56
Penicillins	45.3	45.4	1.00
Cephalosporins	0	0.7	1.00
Carbapenems			
Beta-lactams with beta-lactamase inhibitor	31.2	24.6	0.27
Macrolides	13.3	13.1	1.00
Others	0.7	3.1	0.21

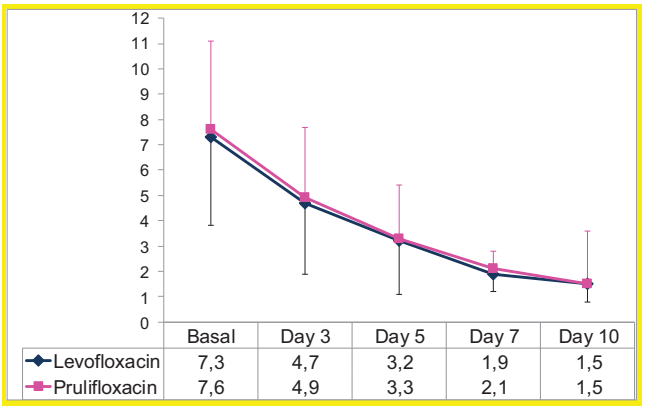

Figure 2. Evolution of the total score of symptomatology of exacerbation of COPD in the two study groups.

(primary study end-point). In both intention-to-treat and per-protocol populations, a slightly higher percentage of success with prulifloxacin was observed; a similar result was noted in the anticipated success rate at Day 7. At Day 10, 35.9% and 36.9% of patients in the levofloxacin and prulifloxacin group had complete resolution of symptomatology.

Forty patients with levofloxacin (31.2%) and 47 with prulifloxacin (36.1%) had new episodes of exacerbation of COPD in the 1-year follow-up (p = 0.51), corresponding to 96 episodes with levofloxacin versus 83 with prulifloxacin; short-term recurrence (within 3 months) was reported in 17.8% (levofloxacin) and 14.2% (prulifloxacin) patients ($p = 0.44$). Death

Table 4. Study outcomes. Results are expressed as percentages, unless otherwise stated. ITT intention-to-treat; PP per-protocol.

Outcome	Levofloxacin ($n = 128$)	Prulifloxacin ($n = 130$)	p value
Primary outcome			
Therapeutic success at day 10—ITT	93.0	96.7	0.62
Therapeutic success at day 10—PP	94.6	99.1	0.21
Secondary outcomes			
Therapeutic success at day 7	28.9	33.8	0.42
Decrease of CRP, Days 0–10 (mg/L, mean–n = 117)	5.3	4.9	0.78
3-month re-exacerbation	17.8	14.2	0.75
12-month re-exacerbation	31.2	36.1	0.90
12-month all-cause mortality	8.5	3.9	0.13

Table 5. Adverse drug reactions during the treatment cycle in the two study groups.

Adverse drug reactions	Timing	Serious?
Levofloxacin		
1. Diarrhea	Day 3	Yes
2. Acute renal failure	Day 3	Yes
3. Diarrhea	Day 3	No
Prulifloxacin		
1. Musculoskeletal pain	Day 7	No
2. Acute renal failure	Day 7	Yes
3. Psychomotor agitation, muscular pain, diarrhea	Day 7	No
4. Epigastric pain	Day 3	No
5. Diarrhea	Day 3	No
6. Acute enteritis	Day 10	No

occurred in 11 patients (8.6%) in the levofloxacin and in 5 cases (3.8%) in the prulifloxacin group (Table 4).

During the treatment cycle, suspected adverse drug reactions were reported by the investigators in 3 and 6 patients treated with levofloxacin or prulifloxacin, which were serious in 2 and 1 cases, respectively. Details for the events are reported in Table 5.

Discussion

The natural history of COPD is characterized by repeated acute exacerbations of respiratory symptoms. Early and appropriate treatment of these episodes is associated with improved outcomes (17), but the percentage of patients not responding to a first cycle of antibiotic therapy is not negligible. In our study, levofloxacin 500 mg and prulifloxacin 600 mg both administered once daily for 10 days showed efficacy rates higher than 90%, and were well tolerated in patients not responding to a previous treatment and requiring hospitalization due to worsening clinical conditions. These results seem to be of particular interest since these were obtained in a challenging patient population with a previous antibiotic treatment failure and characterized by a significant burden of co-morbidities. Moreover, only limited data are reported on this specific population. Furthermore, obtaining such a high level of efficacy is of relevance for the subset of COPD patients who require hospitalization for exacerbation of disease, since these patients seem at particularly high risk for poor outcome. Hospitalizations have important social and economic implications as well (18). By the way, a low rate of previous antibiotic use among patients with a COPD exacerbation requiring hospital admission has been reported in the literature (19); therefore, our study population seems once again of interesting originality.

The study hypothesis of non-inferiority of prulifloxacin with respect to levofloxacin was proved in both primary and secondary efficacy end-points, and in both intention-to-treat and per-protocol populations. The group treated with prulifloxacin experienced a slightly (though not statistically significant) higher percentage of success at the end of treatment cycle and, as anticipated, therapeutic success at Day 7. A very similar and high rate of success for levofloxacin and prulifloxacin has been recently reported in the context of primary treatment of severe COPD patients with acute exacerbations of chronic bronchitis (20): taken together, these findings seem to support the role of fluoroquinolones as first- and second-line treatment for AECOPD.

Possible resistance to broad-spectrum antibiotics is a not negligible issue and should be carefully considered. We cannot rule out that resistance occurred in some patients who had no clinical improvement following antibiotic treatment and were enrolled in the FADOI-FLOR project, as well as among subjects who had no therapeutic success when treated with fluoroquinolones in our study. In this perspective, our experience seems not to support, at least in the setting of patients we evaluated, an antibiotic course of less than 7–10 days duration, since in our study cohort only 4.7% of patients (without differences between treatment groups) reached complete and persistent disappearance of symptomatology after 5 days of therapy.

No significant differences between the two drugs were detected also for occurrence of new episodes of exacerbation of COPD during a 1-year follow-up. The percentage of patients with relapses detected in our study seems higher than that reported in the recent study by Blasi et al. (20). One potential explanation is that our study enrolled a more globally complex sample of patients, both older and with more advanced respiratory disease.

In our study, prulifloxacin and levofloxacin had very similar adverse event profiles. Both antibiotics were generally well tolerated and the rate of serious adverse reactions and of premature drug discontinuation due to safety reasons was very low in both groups (1–2%). In patients of advanced age and suffering from concomitant cardiac disease, concerns have been raised for the use of some antibiotics (21, 22). A potential advantage of prulifloxacin may be its superior safety profile for cardiac events, as recently stated by the EMA Pharmacovigilance Working Party (23); however, our study was not designed or powered to evaluate this issue.

One limitation of our study is that only around 40% of patients had a sputum evaluation and culture, and a very small minority had valid microbiological results at baseline. However, it is well known that even by using sophisticated sampling and microbiological techniques, causative agents of exacerbation of COPD can be identified only in a small proportion of patients. Moreover, our study population was made of patients who had already received a course of antibiotic therapy prior to randomization. Regarding the investigator-initiated nature of our study, no double blinding of the treatments was possible; however, the design we adopted (health personnel in charge of monitoring of the patients was different from that who dispensed drugs) allowed a reliable and appropriate assessment of results.

On the other hand, our study has some strengths which may make its results interesting and valid. First, as previously said, very few information are available on the effects of second-line antibiotic therapy of acute exacerbation of COPD. Second, only patients with a severe episode (requiring hospitalization and complying with Anthonisen I or II criteria) and high suspicion of bacterial exacerbation were enrolled. The very high rate of therapeutic success we obtained seems to indirectly confirm the actual presence of a bacterial etiology. Third, the clinical evaluation was based on an "easy-to-use" and previously described clinical score, which allows a good objective measure of response.

In conclusion, few data are available concerning patients with acute exacerbation of COPD, who are unresponsive to previous antibiotic treatment. The FADOI-FLOR study documented

that fluoroquinolones are very effective and well tolerated in the treatment of exacerbations of COPD that failed with other antibiotic treatments. Prulifloxacin showed similar overall efficacy if compared to levofloxacin, and may therefore be considered a potential therapeutic option in this setting. Some preliminary findings (such as a trend toward more rapid efficacy of prulifloxacin) are of potential interest and need further assessment in specifically designed studies.

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Declaration of interest

All the authors Massimo Giusti, Francesco Blasi, Ido Iori, Antonino Mazzone, Francesco Sgambato, Cecilia Politi, Paola Colagrande, Annamaria Casali, Antonella Valerio, Gualberto Gussoni, Erminio Bonizzoni, and Mauro Campanini have declared no conflicts of interest concerning the submitted manuscript.

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Appendix

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