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Research article

Efficacy and Safety of Levofloxacin in Outpatient Treatment of Exacerbations of COPD and Bronchiectasis

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Abstract

Introduction: Majority of the exacerbations of chronic obstructive pulmonary disease (COPD) and bronchiectasis could be treated on outpatient basis. Aim of the study: To assess efficacy and safety of levofloxacin as empirical treatment of exacerbations of COPD and bronchiectasis in outpatient setting. Methods: We performed an observational, non-randomized, open-label study including 74 patients with exacerbation of COPD and 34 patients with exacerbation of bronchiectasis of bacterial origin which met criteria for outpatient treatment. The patients were treated with oral levofloxacin 500 mg once daily for 10 days (COPD exacerbations) and 14 days (exacerbations of bronchiectasis). Efficacy of the treatment was assessed by a number of patients with clinical remission of exacerbation, while the safety was assessed by a number of patients with side effects during the treatment. Results: Clinical remission of exacerbation, i.e. complete resolution of clinical symptoms and signs or their return to their baseline severity, was achieved in 87.8% of patients with COPD, as well as in 82.3% of patients with bronchiectasis. In addition, the mean time to clinical remission of exacerbation in patients with COPD and bronchiectasis was 6.2 and 9.6 days, respectively. Incidence of side effects during the treatment with levofloxacin was 9.4% in patients with COPD and 11.7% in patients with bronchiectasis. Registered side effects were mild and self-limited and did not require premature discontinuation of the treatment with levofloxacin. Conclusion: Our findings confirmed high efficacy and good tolerability of levofloxacin in empirical treatment of exacerbations of COPD and bronchiectasis in outpatient setting.

Keywords: Bacterial exacerbations, bronchiectasis, chronic obstructive pulmonary disease, levofloxacin, outpatient setting

Introduction

Exacerbations are important events in the course of chronic obstructive lung diseases due to their significant impact on the patients' quality of life, disease progression, hospitalization and readmission rates, mortality, and health care costs.

Exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy. Respiratory infections account for up to 80% of COPD exacerbations, of which bacterial infections are involved in around 50-70%. The predominant bacteria recovered from the lower airways in patients with COPD exacerbations are: Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. In addition, atypical bacteria, e. g. Mycoplasma pneumoniae and Chlamidia pneumoniae, are implicated in up to 10% of exacerbations. According to their severity and management, COPD exacerbations are classified as: mild (treated with short acting bronchodilators), moderate (treated with short acting bronchodilators plus antibiotics and/or oral corticosteroids) and severe (requiring hospitalization or visit to emergency room). More than 80% of COPD exacerbations are managed in outpatient setting with pharmacological treatment including short acting bronchodilators, antibiotics and/or corticosteroids. The criteria of Anthonisen, i.e. increased dyspnea, sputum volume and purulence, are still the most important classification system to identify patients likely to be in-

fected with bacterial pathogens based on presentation of clinical symptoms. Current treatment guidelines recommend antibiotic therapy in patients with Anthonisen criteria of type I (all cardinal symptoms) or II (two cardinal symptoms) if increased purulence of sputum is one of the two symptoms [1-5].

As in the patients with COPD, patients with bronchiectasis often experience exacerbations, i.e. episodes of worsening symptoms with increased sputum volume, sputum viscosity, and cough frequency. They can also experience wheezing, chest tightness, pleurisy, and hemoptysis. These events may be due to superimposed viral infections with subsequent clonal expansion of existing bacteria or acquisition of new bacterial pathogens in the lower airway. The pathogens most frequently associated with both stable disease and exacerbations are: Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Pseudomonas aeruginosa, and Staphylococcus aureus. An exacerbation requiring antibiotics in patient with bronchiectasis is defined by deterioriation of three or more of the following symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, and haemoptysis, when clinician determined that a changes in bronchiectasis treatment was required. Generally, exacerbations of bronchiectasis are diagnosed on a basis of clinical symptoms and signs and majority of them, i.e. mild and moderate exacerbations, are treated in outpatient setting, while severe episodes require hospitalization and/or intravenous antibiotics [6-10].

Levofloxacin is a broad-spectrum bactericidal antibiotic of the fluoroquinolones drug class, the left-handed isomer of ofloxacin, exerting its antimicrobial effects via inhibition of bacterial DNA replication, i.e. via the inhibition of two key bacterial enzymes: DNA gyrase and topoisomerase IV. It has a relatively long duration of action in comparison with other antibiotics that allows for once or twice daily dosing.

Spectrum of activity of levofloxacin includes Gram negative (Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Proteus mirabilis, and Pseudomonas aeruginosa), Gram positive (methicillin-sensitive but not methicillin-resistant Staphylococcus aureus, Streptococcus pneumoniae, Staphylococcus epidermidis, Enterococcus faecalis, and Streptococcus pyogenes), atypical bacterial pathogens (Legionella pneumophila, Chlamydophila pneumoniae, and Mycoplasma pneumoniae), as well as Mycobacterium tuberculosis, including Mycobacterium avium complex. Compared to earlier antibiotics of the fluoroquinoline class such as ciprofloxacin, levofloxacin exhibits greater activity towards Gram-positive bacteria but lesser activity toward Gram-negative bacteria, especially Pseudomonas aeruginosa. In oral and intravenous formulations, levofloxacin is indicated in adults for the treatment of various infections caused by susceptible bacteria, including infections of the upper respiratory tract, lower respiratory tract, skin structures, urinary tract, and prostate. An inhalational solution is indicated for the management of cystic fibrosis patients aged 18 years or older with chronic pulmonary Pseudomonas aeruginosa infections. Levofloxacin, along with other quinolones such as moxifloxacin and gatifloxacin, is a member of the third generation of fluoroquinolones, referred to as the "respiratory quinolones" due to improved activity against gram-positive bacteria commonly implicated in respiratory infections [11, 12].

Common side effects of levofloxacin (occurring in more than 1 in 100 people) include nausea, diarrhea, headache, and skin rash. Severe side effects (occurring in equal or less than 1 in 10,000 people) include tendon inflammation and tendon rupture, seizures, psychosis, peripheral nerve damage, and aortic aneurism. Due to aortic aneurism risk in certain patients, levofloxacin and other fluoroquinolones should not to be used in patients at increased risk (those with a history of blockages or aneurisms of the aorta or other blood vessels, uncontrolled hypertension, certain genetic disorders that involve blood vessels change, and the elderly) unless there are no other treatment options available [13-15].

Aim of the present study was to assess efficacy and safety of levofloxacin as empirical treatment of bacterial exacerbations of COPD and bronchiectasis in outpatient setting.

Materials and Methods

Study design and setting

An observational, non-randomized, open-label study was performed in the period September 2021-January 2022 at the Institute for Occupational Health of RN Macedonia, Skopje.

Efficacy of the treatment with levofloxacin was assessed by a number of patients with clinical remission of exacerbation, as well as by a number of days for its clinical remission. Safety was assessed by a number of patients with side effects during the treatment, i.e. side effects which required and did not require discontinuation of the treatment with levofloxacin.

Study subjects

Study subjects included 108 patients with exacerbation of COPD and bronchiectasis of bacterial origin, i.e. 74 patients with exacerbations of COPD and 34 patients with exacerbation of bronchiectasis, 67 males and 41 females, aged 43 to 74 years, who met criteria for treatment on outpatient basis. In more than a half of the patients with COPD exacerbation (60.8%, i.e. 45/74) levofloxacin was administered after a treatment failure with some other antibiotic (aminopenicillin with clavulonic acid, macrolide, or doxycycline). In the other patients with COPD exacerbations, as well as in all patients with exacerbation of bronchiectasis, levofloxacin was administered as an initial treatment.

All participants were informed about the study and their written consent was obtained. In addition, all included patients had no positive epidemiological evidence for Covid-19, nor positive clinical findings or positive molecular test to SARS-CoV-2.

Study protocol

Bacterial exacerbations of COPD and bronchiectasis were diagnosed following actual criteria [1, 7]. All study subjects underwent clinical examination, blood gas measurements, ECG, and laboratory analysis. Chest X-ray was performed by indication in suspected patients to exclude possible pneumonia.

Spirometric measurements were not performed due to the risk of transmission of Coronavirus disease (SARS-CoV-2). According to the American Thoracic Society (ATS) recommendation, pulmonary functional testing in the period of pandemic should

be limited to tests that are only essential for immediate treatment decisions [16].

Following the actual recommendations, microbiological evaluation was not performed in patients with COPD exacerbation (1). Findings from microbiological evaluation of the patients with exacerbation of bronchiectasis done before the start of treatment with levofloxacin were: negative finding in 14 patients (41.1%), Haemophilus influenzae in eight patients (23.5%), Pseudomonas aeruginosa in five patients (14.7%), Moraxella catarrhalis in three patients (8.8%), Streptococcus pneumoniae also in three patients (8.8%), and Staphylococcus aureus in one patient (2.9%).

Classification of smoking status was done by the World Health Organization (WHO) recommendations [17]. The Body Mass Index (BMI) was determined in all study subjects by computed calculation using BMI calculator [18].

After the diagnosis of exacerbation was established all patient were empirically treated with levofloxacin. Patients with COPD exacerbation were treated 10 days with levofloxacin 500 mg once daily per os. They were advised to continue the regular treatment of stable COPD, as well as to use short-acting bronchodilators when needed. Patients with exacerbation of bronchiectasis were treated 14 days with levofloxacin 500 mg once daily per os. Those with regular treatment for bronchiectasis were advised to continue it.

Table 1. Demographics of the study subjects

Characteristic	Patients with COPD exacerbation (n = 74)	Patients with exacerbation of bronchiectasis (n = 34)	P-value*
Male Female M/F ratio	51 (68.9%) 23 (31.1%) 2.2	16 (47.1%) 18 (52.9%) 0.9	0.0297 0.0297
Mean age (years)	59.1 ± 9.4 (45-74)	56.8 ± 10.8 (43-71)	0.246
Mean time after establishing of diagnosis (years)	6.7 ± 2.2 (4-9)	7.1 ± 2.6 (4-11)	0.409
Mean number of exacerbations in the last year	1.7 ± 0.6 (0-4)	3.2 ± 1.3 (1-5)	0.000
BMI Smoking status Current smokers Ex-smokers Passive smokers	25.4 ± 3.7 21 (28.3%) 9 (12.1%) 19 (25.7%)	26.3± 2.6 10 (29.4%) 6 (17.6%) 8 (23.5%)	0.204 0.912 0.444 0.811
Comorbidities Arterial hypertension DM type 2 IHD Osteoarticular disease	12 (16.2%) 8 (10.8%) 6 (8.1%) 11 (14.8%)	6 (17.6%) 5 (14.7%) 3 (8.8%) 6 (17.6%)	0.853 0.884 0.583 0.760

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with certain variable.
COPD: Chronic Obstructive Pulmonary Disease; M: Male; F: Female; BMI: Body Mass Index; DM: Diabetes Mellitus; IHD: Ishaemic Heart Disease.
*Tested by Chi-square test or Fisher's exact test where appropriate (difference in the prevalence) and independent-samples t-test (comparison of mean value).

Study subjects had intermediate visits at 3, 5, 7 and 10 days (patients with COPD exacerbation) and at 3, 5, 7, 10, and 14 days (patients with exacerbation of bronchiectasis) at which their symptoms, as well as eventual side effects of levofloxacin, were evaluated.

The course of exacerbation was assessed as a function of resolution of the symptoms and the treatment was considered to be successful if clinical remission, i.e. complete resolution of symptoms or their return to the baseline severity, was achieved. Treatment with cepodoxime was stopped two days after resolution of the clinical symptoms and signs. Treatment failure was considered if the clinical symptoms and signs did not improve or got worse as it was noted at each intermediate visit or was not resolved at the end of the treatment [19, 20]. The treatment in the patients in whom occurred mild side effects was continued, while the occurrence of moderate or severe side effect was an indication for its discontinuation.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Chi-square test was used for testing difference in the prevalence. Comparison of the mean time to relief of the symptoms and of the mean FEV1 values was performed by independent-samples t-test. A P-value less than 0.05 was considered as statistically significant.

Results

Demographic and other characteristics of the study subjects are shown on Table 1. Percentage of clinical success of the treatment of exacerbation, i.e. complete resolution of clinical symptoms and signs or their return to the baseline severity, in patients with COPD and bronchiectasis was 87.8% (65/74) and 82.3% (28/34), respectively (P = 0.444). As clinical symptoms and signs did not improve in some intermediate visit, levofloxacin was discontinued prematurely in nine patients with exacerbation of COPD, i.e. in four of them the treatment was continued with another antibiotic on outpatient basis, while in five of them the treatment of exacerbation was continued in inpatient setting, and six patients with exacerbation of bronchiectasis. i.e. in two of them the treatment was continued with another antibiotic on outpatient basis, while in four of them the treatment of exacerbation was continued in inpatient setting.

Mean time to complete resolution of clinical symptoms and signs or their return to the baseline severity, varied from 6.2 ± 0.4 days in patients with exacerbation of COPD and 9.6 ± 1.4 days in patients with exacerbation of bronchiectasis (P = 0.000).

Incidence of side effects during the treatment with levofloxacin was 9.4% (7/74) in the patients with exacerbation of COPD and 11.7% (4/34) in the patients with exacerbation of bronchiectasis (P = 0.713). Registered side effects (headache, dizziness, nausea, and epigastric pain) were mild and self-limited and did not require premature discontinuation of the treatment.

Discussion

Majority of exacerbations of COPD and bronchiectasis are bacterial in origin, caused by common respiratory pathogens. As it was shown in a number of studies, the use of antibiotics

in patients with COPD and bronchiectasis exacerbation reduces the risk of disease progression and mortality. In addition, actual recommendation for the optimal choice of antibiotic and length of treatment are somewhat inconsistent. In addition, an important problem in this field is a growing resistance rate to antibiotics commonly used in the treatment of these events.

In the present study we assessed the efficacy and safety of levofloxacin in the outpatient treatment of exacerbations of COPD and bronchiectasis. Study population included patients with exacerbation of COPD and bronchiectasis who met criteria for treatment in outpatient setting. Males were dominant in the group of patients with COPD exacerbation, while in the bronchiectasis group the number of males and females was similar. Both groups had similar mean age and BMI, as well as similar frequency of accompanying diseases. Mean number of exacerbations in the last year was significantly higher in the bronchiectasis group. Similarly to the findings of our previous studies, we found a large proportion of current smokers and passive smokers and a small proportion of ex-smokers in both COPD and bronchiectasis group that indicated still poor effectiveness of anti-smoking strategies and activities [21, 22].

Clinical remission of exacerbation, i.e. complete resolution of the symptoms or their return to the baseline severity, was found in more than 80% of the patients with COPD. In addition, the mean time to the clinical remission was around six days. Similar results were obtained in our previous study including 63 patients with COPD exacerbation that compared efficacy and tolerability of treatment with levofloxacin 500 mg and levofloxacin 750 mg on outpatient basis (clinical remission in more than 80% of the treated patients and mean time to resolution of exacerbation between five and seven days) [23]. Similar results were also obtained in several other studies performed in the last two decades [24-28]. In addition, similar therapeutic success rate in the treatment of COPD exacerbations was found for other fluoroquinolones, such as moxifloxacin, gemifloxacin and prulifloxacin, i.e. fluoroquinolones were considered as potent antibiotics with low prevalence of bacterial resistance by the most respiratory pathogens [29-32].

On the contrast of a number of studies that investigated efficacy and safety of various antibiotic regimens in the treatment of exacerbations of COPD, up to now there is limited evidence about efficacy of antibacterial treatment of exacerbations of bronchiectasis, i.e. there is paucity of evidence for optimal strategies for treatment of exacerbations in these patients. Exacerbation treatment in bronchiectasis is typically based on knowledge of the patient's microbiology, severity, and clinical response [33, 34]. In our study on efficacy and safety of cefpodoxime in outpatient treatment of lower respiratory tract infections that included patients with exacerbations of COPD (59 patients), community-acquired pneumonia (32 patients) and exacerbations of bronchiectasis (35 patients), clinical remission rate of exacerbations of bronchiectasis was 77% [35].

In the present study we found high resolution rate of exacerbations of bronchiectasis (more than 80%) that was similar to the exacerbation resolution rate found in the COPD group as the exacerbation in both diseases are caused by common respiratory pathogens. According to the actual recommendations, duration of the antibiotic treatment of bronchiectasis exacerbation should be 14 days, i.e. longer than the recommended duration of antibiotic treatment of COPD exacerbation (5-7 days). In the present study the mean time for resolution of the symptoms or their return to the baseline severity was around 10 days, i.e. it was significantly longer than the mean time for clinical remission of exacerbations in the COPD group [1, 7]. High efficacy of levofloxacin in the treatment of exacerbations of bronchiectasis was documented in a few studies in this field. In the study that compared efficacy of oral levofloxacin and parenteral ceftazidime in the empirical treatment of exacerbations that included 35 patients with bronchiectasis, Tsang et al. found similar effectiveness of both antibiotics [36]. On the other side, in the study that investigated the prophylactic effect of short-term treatment with levofloxacin and azithromycin including 90 patients with bronchiectasis randomly divided in two equal groups, Moulaei & Falak found significantly lower number of exacerbations and hospitalizations per year in the levofloxaci group [37].

Frequency of side effects related to levofloxacin in the present study was around 10% in both COPD and bronchiectasis group. The side effects which occurred (headache, dizziness, nausea, and gastrointestinal symptoms) were mild and self-limited and did not require discontinuation of the treatment. Similar findings, i.e. side effects incidence around 12%, were obtained in our previous study on tolerability of levofloxacin 500 mg and levofloxacin 750 mg in the outpatient treatment of COPD exacerbations [23].

Results of the present study must be interpreted in context of its limitations. First, the study design, since the study was neither blinded nor randomized and, therefore, can be a subject to possible selection bias. Second, a relatively small number of the study subjects could have certain implications on data obtained and its interpretation. Third, there was not a follow-up period, i.e. we did not register the incidence of relapses after the clinical remission of exacerbation. On the other hand, the study design may be its strength, as it is documented by other real life-studies. Furthermore, the strength of the study could also be the assessment of efficacy of levofloxacin in empirical treatment of exacerbations of bronchiectasis in outpatient setting that is field with still not sufficient evidence.

Conclusion

In conclusion, in an observational, non-randomized, open-label study aimed to assess clinical efficacy and safety of levofloxacin in the outpatient treatment of bacterial exacerbations of COPD and bronchiectasis we found a high clinical success rate and a low incidence of side effects. Our findings confirm the results of several studies that assessed efficacy and safety of levofloxacin in an outpatient treatment of bacterial exacerbations of COPD and bronchiectasis.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. North Macedonia, Skopje gave approval for performing the study and publishing the results obtained (03-0302-1065 - 24.12.2021).

Competing Interests

All authors hereby have declared that no competing interests exist.

Authors Participations

JM, SS and DM participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. TP managed the literature searches and participated in the managing the analyses of the study. JM, SS, DM, AA, and DB participated in data collection. All authors read and approved the final manuscript.

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