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Moxifloxacin in the Outpatient Treatment of Moderate Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

BACKGROUND: Bacterial infections are involved in more than a half of the exacerbations of chronic obstructive pulmonary disease (COPD).

AIM: To evaluate the efficacy and safety of moxifloxacin in the outpatient treatment of moderate exacerbations of bacterial origin in the COPD patients.

METHODS: We performed a prospective, observational study including 64 COPD patients with moderate exacerbation of bacterial origin empirically treated with moxifloxacin. In 31 of them, moxifloxacin was used as an initial antibiotic (Group 1), whereas in 33 of them moxifloxacin was used after treatment failure with another antibiotic (Group 2). All patients have treated 7 days with moxifloxacin 400 mg once daily per os, and they were followed up for 20 days, with an intermediate visit at 3, 5 and 7 days at which the duration of symptoms and the side effects of the drug were evaluated.

RESULTS: We registered high clinical success rate, i.e. the complete resolution of the symptoms or their return to the baseline severity, similar in both groups (84.3% in all study subjects, 83.9% in the Group 1 and 84.8% in the Group 2). The mean time to complete resolution of the cardinal symptoms or their return to the baseline severity was 5.2 ± 1.1 days. Also, the mean time to complete resolution of the certain cardinal symptoms (increased dyspnea, increased sputum volume and increased sputum purulence) or their return to the baseline severity is given 4.9, 4.7 and 4.2 days, respectively. The incidence of adverse effects during the treatment with moxifloxacin in all study subjects was 10.9%, 9.6% in Group 1 and 12.1% in Group 2. There was no serious adverse effect that required discontinuation of the treatment. Relapse during a 20 days follow-up period was registered in 7.4% of the all study subjects with complete resolution of the cardinal symptoms or their return to the baseline severity, i.e. in two patients from both Group 1 and Group 2 (7.6% and 7.1%, respectively).

CONCLUSION: Our findings suggest high efficacy and good tolerability of moxifloxacin in the treatment of moderate COPD exacerbations of bacterial origin.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the course of the disease because they greatly contribute to the rates of hospitalisation and readmission, disease progression and mortality. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 Report, COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy [1]. Respiratory infections, environmental and occupational exposures, discontinuation of the regular treatment, and worsening of the comorbid conditions are considered as causes of exacerbations, but in up 20% of the cases, the cause of exacerbation remains unknown [2] [3].

The goals of treatment for COPD exacerbations are to minimise the negative impact of the current exacerbation and prevent the development

of subsequent events. 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 oral corticosteroids) and severe (requiring hospitalisation or visit to the emergency room). Depending on the severity of an exacerbation and/or the severity of the underlying disease, an exacerbation can be managed in an outpatient or inpatient setting. More than 80% of COPD exacerbations are managed in an outpatient setting with pharmacological treatment including short-acting bronchodilators, antibiotics and/or corticosteroids [1].

Respiratory infections account for up to 80% of exacerbations, of which bacterial infections are involved in around 50-70%. The predominant bacteria recovered from the lower airways in patients with chronic bronchitis (CB) and COPD exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenza,* and *Moraxella catarrhalis.* Atypical bacteria, e. g. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are implicated in up to 10% of exacerbations [4] [5]. 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 infected with bacterial pathogens based on the presentation of clinical symptoms [6] [7] [8]. 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 and in patients who require mechanical ventilation (invasive or non-invasive). The choice of the antibiotic is based on the local bacterial resistance pattern. Usually, initial empirical treatment is an aminopenicillin with clavulanic acid, macrolide, or doxycycline. The recommended length of antibiotic therapy is 5-7 days. Resolution of exacerbation is considered as a complete resolution of cardinal symptoms or their return to the baseline severity [1] [9] [10].

Moxifloxacin is a fourth generation fluoroquinolone with a broad spectrum of activity against a wide range of the microorganisms, including Gram-positive and Gram-negative bacteria, atypical pathogens, and anaerobic bacteria, i.e. against nearly all treatable bacteria associated with COPD exacerbations, including *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis*, most *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, etc. Also, moxifloxacin may be regarded as the most excellent tissue ability. Common side effects associated with the use of moxifloxacin are abdominal discomfort, nausea, vomiting, diarrhoea, headache, dizziness, blurred vision, anxiety, and skin itching. Serious side effects of moxifloxacin which occur rarely include severe diarrhoea, acute allergic reactions, connective tissue problems (tendon rupture and joint problems), muscle pain, confusion, agitation, depression, and prolonged QT heartbeat interval [11] [12] [13].

The present study aims to evaluate the efficacy and safety of moxifloxacin in the outpatient treatment of moderate bacterial exacerbations in COPD patients.

Material and Methods

A prospective, observational study (a real life-study) including 64 COPD patients with moderate exacerbation with clinical presentation suggesting bacterial origin, 39 males and 25 females, aged 43 to 77 years. The diagnosis of COPD in all patients was established according to the actual GOLD criteria [1]. All participants were informed about the study, and their written consent was obtained.

The study was carried out in the period August 2017-November 2017 at the Institute for Occupational Health of R. Macedonia, Skopje-WHO Collaborating Center. The study of the effects of various antimicrobial regimens on the clinical course of exacerbations of chronic bronchitis and COPD carried out by Miravittles et al., [14] was used as a model.

Including criteria was the presence of a moderate exacerbation of probably bacterial origin which can be managed on an outpatient basis. The diagnosis of bacterial exacerbation was defined by the patient's symptoms, using the criteria described by Anthonisen et al., [6]. Also, all patients underwent clinical examination, spirometry, blood gas measurements, ECG, and laboratory analysis. Chest X-ray was performed in a part of the patients by indications.

Excluding criteria were mild and severe exacerbations, patients with exacerbation type III (one cardinal symptom) or type II if increased purulence of sputum was not one of the two symptoms, patients with asthma, cystic fibrosis, malignancy, pneumonia and pulmonary embolism and patients with known hypersensitivity to moxifloxacin.

All study subjects were treated 7 days with moxifloxacin 400 mg once daily per os. In about a half of the patients enrolled in the study (31/64) moxifloxacin was given as an initial empirical treatment (Group 1), whereas in the rest of the study subjects (33/64) moxifloxacin was given after treatment failure with other antibiotic (aminopenicillin with clavulanic acid, clarithromycin, or doxycycline) (Group 2). The study subjects were advised to continue the regular treatment of stable COPD, as well as to use short-acting bronchodilators when needed. All study subjects had intermediate visits at 3, 5 and 7 days at which they were evaluated about the duration of symptoms and the side-effects of the drug.

The course of exacerbation was evaluated as a function of the resolution of the symptoms, and the treatment was considered to be successful if complete resolution of cardinal symptoms or their return to the baseline severity was achieved. In addition, spirometric parameters, i.e. forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, mean expiratory flow at 50% of FVC (MEF_{50}), mean expiratory flow at 75% of FVC ($MEF7_{75}$), and mean expiratory flow at 25-75% of FVC (MEF_{25-75}), at the first visit and at the end of the treatment were compared. Relapse rates were registered during a 20 days follow-up period in the patients with remission of the symptoms.

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 the mean FEV_1 values was performed by independent-samples *t*-test. A *P*-value less than 0.05 was considered as statistically significant.

Results

The characteristics of the study subjects are shown in Table 1.

Table 1. Characteristics of the study subjects

Variable	Study subjects (n = 64)
Males	39 (60.9%)
Mean age (years)	53.4 ± 9.3
Mean duration of COPD (years)	12.1 ± 5.7
COPD severity*	
GOLD 2 (50% ≤ FEV_1 < 80% predicted)	34 (53.1%)
GOLD 3(30% ≤ FEV_1 < 50% predicted)	30 (46.9%)
Type of exacerbation**	
Type I	35 (54.7%)
Type II	29 (45.3%)
Increased dyspnea	53 (82.8%)
Increased sputum volume	47 (73.4%)
Increased sputum purulence	64 (100%)
Smoking status***	
Current smokers	18 (28.1%)
Pack-years smoked	11.7 ± 4.3
Ex-smokers	21 (32.8%)
Passive smokers	14 (21.8%)
Comorbidities	
Arterial hypertension	23 (35.9%)
Depression	10 (15.6%)
Diabetes mellitus type 2	7 (10.9%)

Numerical data are expressed as a mean value with standard deviation; the frequencies as a number and percentage of examinees with a certain variable. COPD: chronic obstructive pulmonary disease: GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 second. * COPD severity was defined according to the severity of airflow limitation [1]; ** Type of exacerbation was defined according to the Anthonisen et al., [6] classification; *** Classification of smoking status was done according to the World Health Organization recommendations [15].

Moxifloxacin was not discontinued prematurely in any patient enrolled in the study. The percentage of clinical success (i.e. complete resolution of the cardinal symptoms or their return to the baseline severity) in all study subjects was 84.3% (54/64) being similar in the study subjects of both Group 1 (83.9%, i.e. 26/31) and Group 2 (84.8%, i.e. 28/33) (Figure 1).

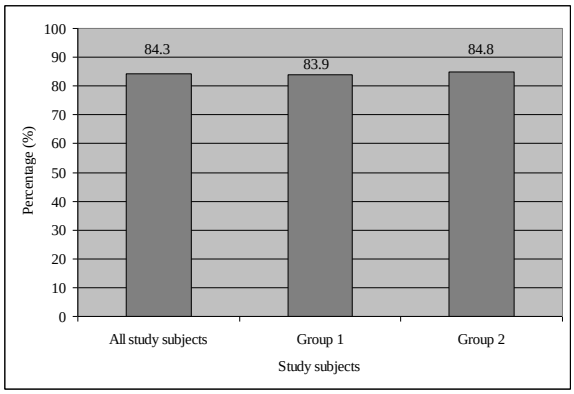

Figure 1: the Clinical success of the treatment with moxifloxacin

The mean time to complete resolution of the cardinal symptoms or their return to the baseline severity was 5.2 ± 1.1 days. The mean time to complete resolution of the certain cardinal symptoms or their return to the baseline severity is given in Figure 2.

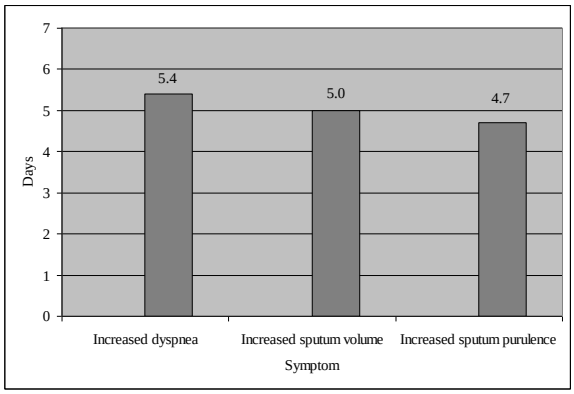

Figure 2: Mean time to complete resolution of the certain cardinal symptoms or their return to the baseline severity

Mean values of the measured spirometric parameters after the treatment with moxifloxacin were significantly higher as compared to their pre-treatment mean values (Table 2).

Table 2: Pre-and post-treatment mean values of the spirometric parameters

Spirometric parameter	Pre-treatment mean value (% pred)	Post-treatment mean value (% pred)	*P*-value
FVC	69.4 ± 8.7	74.3 ± 9.1	0.0023
FEV_1	50.1 ± 7.4	54.7 ± 6.7	0.0003
FEV_1/FVC ratio	0.57 ± 0.05	0.61 ± 0.03	0.0000
MEF_{50}	43.5 ± 9.7	49.2 ± 10.2	0.0015
MEF_{75}	34.1 ± 11.3	38.3 ± 9.4	0.0239
MEF_{25-75}	62.4 ± 10.8	68.1 ± 11.2	0.0040

% pred: % of predicted value; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; MEF_{50}: mean expiratory flow at 50% of FVC; MEF_{75}: mean expiratory flow at 75% of FVC; MEF_{25-75}: mean expiratory flow at 25-75% of FVC.

The incidence of adverse effects during the treatment with moxifloxacin in all study subjects was

7.8% (5/64), 6.5% in the Group 1 (2/31) and 9.1% in the Group 2 (3/33) (Figure 3). Registered side effects were mild and self-limited, i.e. there was no serious adverse effect that required discontinuation of the treatment. Dyspeptic problems (nausea, vomiting, and epigastric pain), headache and dizziness were the most frequent adverse events.

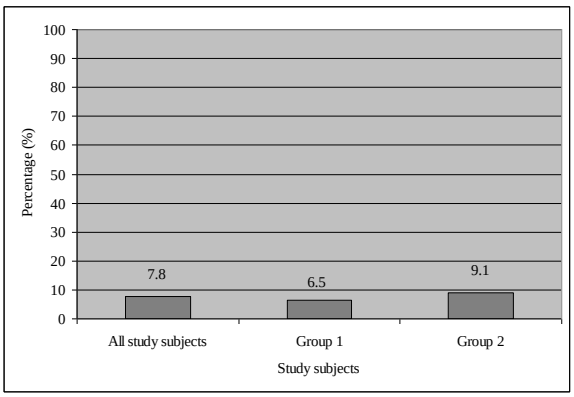

Figure 3: Incidence of adverse effects during the treatment with moxifloxacin

Relapse during a 20 days follow-up period was registered in 7.4% of the all study subjects with complete resolution of the cardinal symptoms or their return to the baseline severity (4/54), i.e. in two patients from both Group 1 and Group 2 (7.6% and 7.1%, respectively) (Figure 4).

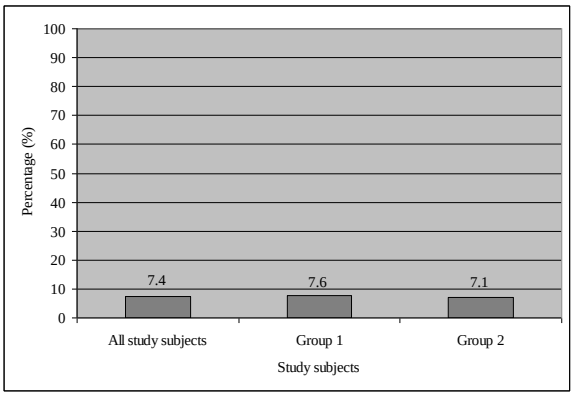

Figure 4: Incidence of relapses after treatment with moxifloxacin during 20 days follow-up period

Discussion

COPD is one of the leading causes of morbidity and mortality worldwide that induces substantial and increasing economic and social burden. Also, exacerbations are the most frequent cause of hospitalisation and death in patients with COPD, so their treatment and prevention have great importance in the management of the disease.

In the present study, we assessed the efficacy and safety of moxifloxacin in the outpatient treatment of moderate COPD exacerbations with clinical manifestations indicating bacterial origin. The diagnosis of exacerbation was based on the presence of clinical symptoms and lung function measurements without microbiological evaluation of the sputum. According to the actual recommendations, sputum analysis should be reserved for patients with frequent exacerbations and for chronic purulent sputum in whom the presence of more virulent and/or more resistant bacteria is likely [3] [9] [16]. Moxifloxacin was an initial treatment in about a half of the study subjects, whereas in the rest it was given following treatment failure with amoxicillin with clavulanic acid, clarithromycin, or doxycycline. We found a large proportion of active and passive smokers among examined subjects that was similar to its prevalence in adults documented in our previous studies [17] [18].

Results of the present study indicated a high clinical success rate (84.3%) and time-course of the recovery (5.2 days). Similar results were obtained in our study on efficacy and tolerability of eight antimicrobial regimens in the outpatient treatment of exacerbations of COPD performed in 2013. Namely, the clinical success rate for moxifloxacin in that study was 80.9%, while the mean time for complete resolution of the symptoms of exacerbation or their return to the baseline severity was 5.7 days [19] [20]. Furthermore, results indicating a high efficacy of moxifloxacin in the treatment of COPD exacerbations were obtained in several other studies. In the meta-analysis of 11 randomized controlled studies Kai-Xiong et al. found that moxifloxacin was as clinically equivalent and bacteriologically superior to the antibiotic regimens routinely used in patients with exacerbations of CB and COPD and concluded that therapy with moxifloxacin might be a promising and safe alternative to empirical treatment for CB and COPD exacerbations [21]. Also, in the comparison of the efficacy of oral moxifloxacin versus other intravenous antibiotics in patients with COPD exacerbations requiring urgent admission, Juan Pator et al., found that *ab initio* oral moxifloxacin is an effective alternative to other intravenous antibiotics (amoxicillin with clavulanic acid, ceftriaxone, or levofloxacin) [22].

In a prospective observational study conducted in eight Eastern European countries including 2,536 patients older than 35 years with CB or COPD exacerbation treated with moxifloxacin for 5, 7 and 10 days, Chuchalin et al., reported *very good* or *good* efficacy in 97.7% of the treated patients, *sufficient* in 1.8%, and *insufficient* in 0.5% [23]. In the Moxifloxacin in Acute Exacerbations of Chronic Bronchitis Trial (MAESTRAL), Wilson et al., found significantly lower clinical failure rates in the patients with COPD exacerbations treated with moxifloxacin as compared to the patients treated with amoxicillin with clavulanic acid [24].

There is consistent evidence that the most

commonly associated side effects of antibiotics used in the treatment of COPD exacerbations are gastrointestinal and that the risk of *Clostridium difficile*-associated diarrhoea may be increased with antibiotic use [25]. In the present study, we found a low incidence of mild side effects during the moxifloxacin treatment (7.8%) that did not require its discontinuation. Similar incidence and severity of the adverse effects during moxifloxacin therapy were found in our study performed in 2013 (7.1%) [19]. The incidence of side effects ranging from 4 to 12% is reported in several studies on the safety of moxifloxacin during treatment of COPD exacerbations [21] [24] [26]. In the study performed by Chuchalin et al. reported incidence of serious adverse effects during moxifloxacin treatment (atrial fibrillation, acute myocardial infarction, diplopia, allergic oedema, amnesia, and skin reaction) considered to be drug-related was 0.15% [23].

One of the main goals of treatment of COPD exacerbations is to prevent the development of subsequent events as exacerbations can cluster in time, and once a COPD patients experience an exacerbation, they will show increased susceptibility to another event [1] [27]. In the present study, the incidence of relapses during the follow-up period was 7.4%. Several studies indicated a low incidence of relapses after the treatment of COPD exacerbations with moxifloxacin and a prolonged time to the next exacerbation [28] [29] [30].

The present study must be interpreted within the context of its limitations. First, the results obtained should be viewed with caution, since the study was neither blinded nor randomised and, therefore, can be a subject to possible selection bias. On the other hand, the study design may be its strength, as it is documented by other real life-studies. Second, a relatively small number of the study subjects could have certain implications on the data obtained and its interpretation. Third, the short follow-up period could also have certain implications on the data obtained and its interpretation.

In conclusion, in a prospective, observational study on efficacy and tolerability of moxifloxacin in the treatment of moderate exacerbations of COPD in the outpatient setting, we found high clinical success rate and low incidence of side effects indicating good tolerability. Our findings suggest that moxifloxacin can be used as a first choice antibiotic in the outpatient treatment of moderate bacterial exacerbations of COPD.

Ethical Approval

The Ethical Committee of the Institute of Occupational Health of R. Macedonia, Skopje – WHO Collaborating Center and GA^{2}LEN Collaborating Center approved for performing the study and publishing the results obtained (0302-619-04.09.2017).

Authors Participations

JM participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. JKB participated in the study design, writing the protocol, managing the analyses of the study, as well as writing all versions of the manuscript. TP managed the literature searches and participated in managing the analyses of the study. KV performed the statistical analysis and participated in the managing of the analyses of the study. SS and DM participated in the data collection. All authors read and approved the final manuscript.

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