Moxifloxacin versus Standard Therapy in Patients with Pneumonia Hospitalized after Failure of Preclinical Anti-infective Treatment

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Abstract

The failure rate of primary empirical anti-infective treatment of community-acquired pneumonia is reported to range between 2 and 7%. These patients are subject to a greater risk of intensive medical treatment and a higher mortality rate than patients who respond to primary treatment. We investigated 63 patients in a "real life scenario" who were admitted to the hospital after failure of primary outpatient therapy for community-acquired pneumonia. Thirty-three patients received intravenous standard therapy (betalactam 14, macrolide 3, levofloxacin 6, doxycycline 1, combinations 9 patients) while 30 patients were treated with intravenous moxifloxacin. The oral antibiotic pretreatment that failed most frequently was clarithromycin (n = 25), followed by amoxicillin/clavulanic acid (n = 16), cefixime (n = 10), cefuroxime/axetil (n = 5), doxycycline (3), cefpodoxime, and ciprofloxacin (2 each). There were no differences between the two groups in respect of age, gender, numbers of patients in nursing homes, numbers of patients with different underlying diseases (chronic bronchitis, coronary heart disease, diabetes mellitus, smoking, etc.), severity of pneumonia at the time of admission, numbers of patients requiring intensive care, and lethality. The group that underwent standard therapy experienced failure of the empirical intra-hospital antibiotic therapy more often during therapy [10 (30%) patients vs 2 (6%) in the moxifloxacin group, p = 0.009] and clinical failure of treatment on day 28 after initiation of therapy [7 (21%) patients vs 2 (6%) in the moxifloxacin group, p = 0.003]. In cases of failure of empirical preclinical antibiotic treatment for community-acquired pneumonia, subsequent intra-hospital treatment with moxifloxacin is more successful than standard therapy in our study reflecting a "real life scenario".

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Introduction

Pneumonia is one of the leading causes of death throughout the world. In Austria about 20,000–40,000 persons develop pneumonia every year; a large number of these are treated outside hospitals. Anti-infective treatment is empirical in nature when an initial microbiological culture is not available and/or the cause of pneumonia has not been established. Anti-infective treatment is conducted in accordance with the guidelines of various medical societies and is usually successful [1, 2]. In cases of hospitalized patients, pneumonia improves slowly in 10–20% [3–5] while a further 10% experience life-threatening complications in conjunction with progressive pneumonia [6, 7].

Failure rates are markedly lower for outpatients under treatment who have previously visited emergency outpatient departments and/or doctors' offices. One study [8] reports a hospitalization rate of 2.2% within 3 weeks after an initial visit to an emergency outpatient department. Two other reports in which therapy failure was defined rather differently show that about 7% of patients who were primarily treated in the outpatient department later had to be admitted to the hospital [9, 10]. A further very large prospective study of community-acquired pneumonia reports a therapy failure rate of 6%; in this investigation, therapy failure was defined as the absence of response or the deterioration of clinical or radiological signs within 48–72 h after primary treatment with oral antibiotics, leading to a modification of the anti-infective treatment or to invasive investigations [11]. However, delayed healing of pneumonia was also associated with patient-related factors such as advanced age, alcoholism, and the presence of various underlying diseases [12, 13].

Since the first description of a penicillin-resistant pneumococcus in Australia in 1967, antimicrobial resistance to pneumonia germs has become very widespread. In Austria

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as well, resistance to the pathogens causing pneumonia is reported to be on the increase [29]. In contrast to betalactams and macrolides, currently moxifloxacin is microbiologically effective with regard to nearly all relevant typical and atypical pathogens causing pneumonia. In a recent multicenter study in Austria which comprised 1,385 isolates, the maximal inhibitory concentration (MIC) of moxifloxacin was ≤ 0.5 mg/l; in other words, its resistance rate was 0% [29].

We investigated 63 consecutive patients under "real life conditions" who had to be admitted to one of the regular wards of the University Hospital in Graz because of community-acquired pneumonia due to the failure of outpatient oral antibiotic therapy. Thirty-three patients received intravenous (iv) standard therapy (betalactam 14, macrolide 3, levofloxacin 6, doxycycline 1, combinations 9 patients) while 30 patients were treated with iv moxifloxacin 1 × 400 mg. The primary purpose of the investigation was to compare standard therapy with moxifloxacin regarding clinical cure/failure rates after start of intra-hospital therapy and cure/failure rates of intra-hospital therapy 28 days after initiation of intra-hospital therapy.

Methods

This study is a prospective randomized study of 63 patients with community-acquired pneumonia, who had been admitted to a regular ward of the Department of Medicine, University Hospital Graz.

The following inclusion criteria had to be fulfilled: age 18 years or above, acute start of one or more clinical symptoms of pneumonia (cough, fever, expectoration, dyspnea, etc.), a new radiological infiltrate within 24 h after the start of typical symptoms of pneumonia. Only those patients who had been hospitalized because of pneumonia-related complications, such as deterioration of the signs and symptoms of pneumonia under ongoing preclinical antibiotic therapy, were included in the study.

Patients who had to be admitted for the management of diseases other than pneumonia (e.g., due to comorbidities such as coronary heart disease or hyperglycemia in the presence of diabetes mellitus, etc.) were not included in the analysis even if they had pneumonia simultaneously. In addition, patients with immunosuppressive medication and or disease (HIV, neutropenia, neoplastic disease, transplantation, etc.), patients receiving moxifloxacin in the previous 30 days, and patients with fatal underlying diseases were excluded.

After randomization, the patients received either therapy according to the decision of the admitting physician (all antibiotics with the exception of moxifloxacin were permitted) or were given moxifloxacin intravenously 1 × 400 mg.

Microbiological investigations on admission [sputum Gram stain, sputum culture, urinary antigen test for legionella and pneumococci (BINAX, Scarborough, ME, USA), etc.] were left to the discretion of the admitting physician.

The following data were registered: duration of hospitalization, nature of discharge (sent home, to a nursing home, or death), gender, height, weight, source of transfer (home, nursing home), underlying diseases: chronic bronchitis, coronary heart disease, diabetes mellitus, heart failure, smoking; type, dose and duration of the anti-infective therapy given prior to admission; leukocyte count, CRP at admission, all data pertaining to the Pneumonia Severity Index (PSI) [14]. In accordance with this recommendation, the classes 1–3 and 4–5 were grouped together for the present analysis.

The primary endpoint was clinical failure after start of therapy and failure of therapy 28 days after initiation of intra-hospital therapy. Failure on therapy was defined as non-responsive pneumonia (the persistence of fever (above 38°C) or clinical symptoms (dullness, cough, sputum, dyspnea) for at least 72 h after the start of antimicrobial therapy) and/or progressive pneumonia (clinical deterioration, such as the development of acute respiratory insufficiency requiring artificial respiration, or septic shock after 72 h following the start of antimicrobial therapy). For the determination of failure rates on day 28 death and progressive pneumonia and/or pleural empyema war additional definitions of failure.

Secondary endpoints were: admission to an intensive care unit (secondarily after more than 48 h of hospitalization), the failure of empirical intra-hospital therapy (standard therapy vs moxifloxacin) and the need for additional antibiotic therapy, lethality, and the duration of hospitalization. Furthermore, the results of microbiological tests with regard to the presence of microbiological resistance to the oral antibiotic therapy given prior to admission were investigated.

Statistical Analysis

Categorical variables in the two groups were analyzed by means Chi square statistics. The t-test was used for continuous variables. Two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 102 patients who had been initially treated on an outpatient basis and had to be admitted to the hospital subsequently because the outpatient treatment had failed, were screened during the period of the study. Of these, 39 were excluded because of exacerbation and/or deterioration of the underlying disease and 63 could be included because of non-responsive pneumonia (the persistence of fever (above 38°C) or clinical symptoms (dullness, cough, sputum, dyspnea) for at least 72 h after the start of antimicrobial therapy) and/or progressive pneumonia pneumonia (clinical deterioration) (Table 1). Thirty-three patients received treatment according to the decision of the admitting physician (Table 2) while 30 patients were treated with moxifloxacin. There were no differences between the groups in respect of age, gender distribution, height or weight, numbers of patients in nursing homes, or underlying diseases such as COPD, coronary heart disease, heart failure, neoplasms, diabetes, and smoking.

The initial antibiotic treatment had been administered 1–8 days prior to admission. The most commonly administered drugs were clarithromycin, amoxicillin/clavulanic acid, and cefixime. Cefuroxime/axetil, cefpodoxime, doxycycline, and ciprofloxacin were administered less frequently (Table 3).

The severity of pneumonia, laboratory values and the result of extra- and intra-hospital anti-infective secondary and tertiary therapy are listed in Table 3. At the time of admission the inflammatory parameters (leukocytosis, CRP) and the severity of pneumonia were comparable in

Table 1
Demographic data of the two groups (means ± SD or absolute value and %).

Parameter	Standard therapy (n = 33)	Moxifloxacin (n = 30)	p-value
Age	67 ± 20	69 ± 15	0.56
Gender (m/f)	9/24	10/20	0.34
Height (cm)	165 ± 9.7	164 ± 7.1	0.53
Weight (kg)	66 ± 15	66 ± 14	0.33
Nursing home (%)	6 (19%)	5 (20%)	0.48
COPD	12 (39%)	11 (37%)	0.53
CHD	11 (36%)	10 (33%)	0.53
Heart failure	16 (48%)	15 (50%)	0.54
Neoplasms	3 (9%)	4 (13%)	0.46
Diabetes	14 (45%)	15 (50%)	0.55
Smoking	10 (30%)	12 (40%)	0.43

Table 2
Antibiotic treatment according to the decision of the admitting physician ("standard therapy").

Antibiotic	Intravenous		
	Total (n = 33)	Daily dose (mg)	Duration (days)
Clarithromycin	3	1,000	2–9
Amoxicillin/clavulanic acid	6	3,300–6,600	6–15
Ceftriaxone	4	2,000	8–14
Cefuroxime	4	4,500	8–15
Doxycycline	1	200	8
Levofloxacin	6	500–1,000	5–16
Combinations:			
Amoxicillin/clavulanic acid plus clarithromycin	6	6,600 plus 1,000	4–13
Cefuroxime plus clarithromycin	3	4,500 plus 1,000	7–14

Table 3
Antibiotic pretreatment.

Antibiotic	Standard therapy			Moxifloxacin		
	Total (n = 33)	Daily dose (mg)	Duration (days)	Total (n = 30)	Daily dose (mg)	Duration (days)
Clarithromycin	13	250–500	2–8	12	250–500	1–7
Amoxicillin/clavulanic acid	8	1,825–2,000	4–5	8	1,825–2,000	4–5
Cefixime	6	400–800	1–7	4	400–800	1–3
Cefuroxime/axetil	2	1,000	7	3	1,000	4–5
Doxycycline	1	200	4	2	200	4–5
Ciprofloxacin	2	500	5	–	–	–
Cefpodoxime	1	400	1	1	400	3

both groups (Table 4). The risk class 4–5 was present in 77% of the standard therapy group and 70% of the moxifloxacin group (p = 0.58).

An additional antibiotic course for failing intra-hospital therapy was necessary in ten cases (non-responsive pneumonia: six, progressive pneumonia: four) in the standard therapy group and in two cases in the moxifloxacin group (progressive pneumonia: two) (p = 0.009). Clinical intra-hospital therapy failure on day 28 after initiation of treatment was registered in seven cases in the standard therapy group and in two cases (one patient with pleural empyema necessitating surgery an a complicated postoperative course, and one patient with progressive pneumonia due to nosocomial infection) in the moxifloxacin group (p = 0.003). The difference in the failure rates in the "standard therapy" group is related to the time of failure. Ten patients failed during therapy, and seven failed within 28 days (five due to death, two due to persistent pneumonia with pleural empyema necessitating surgery).

During the subsequent course of hospitalization, 18–26% of patients in either group had to be admitted to the intensive care unit within the first 3 days of hospitalization (p = 0.33). Inadequate microbiological treatment prior to inclusion was given in three cases in the standard therapy group and in four cases in the moxifloxacin group (Table 4.). Lethality, the duration of hospitalization, and the nature of discharge (the patient's home or a nursing home) were similar in both groups (Table 4).

Discussion

The present study provides insight into the state of pneumonia treatment in medical practice for doctors who are involved in the distribution of resources and for administrators who monitor the quality of medical work. Sixty-three patients who had been admitted to the hospital because of failure of antibiotic therapy prescribed by a practicing doctor were investigated.

The treatment with moxifloxacin in the hospital led to a better outcome than did standard therapy with other

Table 4
Severity at the time of admission, laboratory data, outcome of treatment.

Parameter	Standard therapy (n = 33)	Moxifloxacin therapy (n = 30)	p-value
Leukocytes (g/l)	15.2 ± 12.5	13.2 ± 6.7	0.39
CRP (g/l)	137 ± 111	142 ± 92	0.34
PSI[a]	118 ± 55	127 ± 36	0.23
Risk class at admission:			
I–III	11 (33%)	10 (30%)	0.58
IV–V	22 (67%)	20 (70%)	
Admission to the ICU within 72 h	6 (18%)	8 (26%)	0.33
Failure of initial intra-hospital therapy during treatment[b]	10 (30%)	2 (6%)	0.009
Microbiology:			
Staphylococcus aureus	2	3	
Streptococcus pneumoniae	1	2	
Pseudomonas aeruginosa	1	0	
Klebsiella pneumoniae	1	1	
Haemophilus influenzae	1	2	
Negative	8	7	
Not available	19	15	
Preclinical therapy microbiologically inadequate/adequate/not available	3/1/30	4/3/23	
Clinical therapy failure (day 28)	7 (21%)	2 (6%)	0.003
Cure	26 (78%)	27 (90%)	0.56
Death due to any cause	5 (15%)	3 (10%)	0.20
Death due to pneumonia	4 (12%)	2 (9%)	0.43
Discharge:			
To go home	22	25	0.42
To the nursing home	7	5	0.29
Duration of hospitalization	11.7 ± 8.3	9.1 ± 4.0	0.11

[a] PSI according to *Fine* et al. [14]
[b] Failure of empirical intra-hospital therapy and the need for additional antibiotic therapy

substances. Furthermore, an additional anti-infective therapy was required less often when moxifloxacin was administered. The failure of antibiotic therapy started on an outpatient basis is associated with a poorer intra-hospital medical outcome than adequate primary treatment [11]. The authors of this study [11] believed that failure rates and subsequent admission to hospital occur more commonly among patients who are examined in an emergency outpatient department than among those initially treated by practicing physicians. However, primary (ultimately failing) empirical therapy leading to hospitalization was prescribed in all cases by practicing physicians and not in an emergency outpatient department in our study.

However, it should be noted that neither the failure of initial therapy nor the poor outcome of such therapy necessarily implies that the treatment provided by the practicing physicians is of poor quality. A well-known fact is that a small percentage of patients with a very low risk of complications secondary to pneumonia, who will definitely have primarily low PSI scores, must be admitted later on to the hospital [15]. However, if the number of therapy failures which have to be subsequently treated in the hospital increases, the appropriateness of the initial treatment decision may well be questioned. This is especially true if the patient develops significant complications (intensive care treatment, lethality, etc.) later on. This was the case in the present study. Medical management processes can be improved by identifying the cause of failed treatment; the present investigation showed that the quest for the cause must be started at the practicing physician's office [16].

In the case of pneumonia, poor response to empirical therapy may be due to several causes [17]. It is not known whether the practicing physician conducts an adequate differential diagnosis in every patient who presents with signs of pulmonary infection. Very few studies have actually investigated the causes of treatment failure in cases of pneumonia [18–28]. One study reported failure of treatment in 11% (49 of 440 patients) of patients with community-acquired pneumonia [19]. The investigators divided therapy failures into non-responsive pneumonia and progressive pneumonia. Non-responsive pneumonia was defined as the persistence of fever (above 38°C) or clinical symptoms (dullness, cough, sputum, dyspnea) for at least 72 h after the start of antimicrobial therapy. Progressive pneumonia was defined as clinical deterioration, such as the development of acute respiratory insufficiency requiring mechanical ventilation, or septic shock after 72 h following the start of antimicrobial therapy. Primary persistent or nosocomial infection was the cause of failure in about 75% of the patients. The majority of patients who did not respond to the primary treatment had primary or persistent infections while nosocomial infections were usually associated with progressive pneumonia. Less than 20% of the patients subsequently had a non-infectious process. In a

further study, failure of therapy was registered in 81 hospitalized patients with community-acquired pneumonia, from a total of 1,383 non-immunosuppressed patients. In 32% the etiology was unknown, while *Streptococcus pneumoniae* was found in 22% and *Legionellae* in 21%. The investigators concluded that the presence of *Legionellae* and/or a high PSI (> 90), multilobular infiltrates, gram-negative pneumonia and inadequate antimicrobial therapy increase the likelihood of therapy failure. Antimicrobial resistance, unusual pathogens, other complications or side effects of drugs, are responsible for a small number of therapy failures. In our study, clinical intrahospital therapy failure on day 28th after initiation of treatment was 21% in the standard therapy group and 6% in the moxifloxacin group (p = 0.003) and an additional antibiotic course was administered in 30% in the standard therapy group and in 6% in the moxifloxacin group (p = 0.009). These higher failure rates could be due to the fact that patients failing primary therapy on an outpatient basis have higher failure rates of inpatient iv therapy in patients treated with "standard therapy".

In our study as well, the small number of cases of resistant pathogens (n = 7) did not permit a final conclusion about the role of the microbial ineffectiveness of primary anti-infective therapy in treatment failure and, eventually, the outcome of the treatment. This is also true for the subsequent failure of secondary treatment with standard antibiotics. Nevertheless, the better microbiological effect of moxifloxacin is evidenced by its better clinical efficacy versus standard therapy in respect of local resistance data (cf. resistance report of the Medical University of Graz, Isolates from the respiratory tract 2004 [http://www.hygiene-graz.at/bakteriologie/frameset.html]: pneumococci (n = 143): 9% penicillin resistance, 19% erythromycin-resistant, 0% moxifloxacin resistance; *Staphylococcus aureus* (n = 188): 7.4% methicillin-resistant, 14.4% erythromycin-resistant, 75% penicillin-resistant, 0% moxifloxacin-resistant; hemophilus 8.6% amoxicillin-resistant, 0% moxifloxacin resistance) [30].

The antibiotics used for outpatient therapy of CAP belong to various antibiotic classes and naturally reflect the local "mode of prescription". Notably, clarithromycin led to therapy failure more often, although a clarithromycin-resistant pathogen was found to be the cause in only three of ten cases. Remarkably, all of these patients had been previously treated with oral clarithromycin and all of the isolated bacteria were *Haemophilus influenzae*. The significance of under dosage of this medication with 500 mg o.d. p.o. in cases of severe pneumonia (mean PSI, 118!) should be emphasized [27]. In cases of failure of empirical preclinical antibiotic treatment for community-acquired pneumonia, subsequent intra-hospital treatment with moxifloxacin is more successful than standard therapy in our study reflecting a "real life scenario". However, further studies are needed to confirm this result.

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