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Identifying patients at risk of late recovery (≥8 days) from acute exacerbation of chronic bronchitis and COPD

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Summary
Objectives: To identify factors associated with late recovery (≥8 days from exacerbation start) in patients with acute exacerbations of chronic bronchitis/COPD (AECB/AECOPD).
Methods: An international, observational, non-interventional study in outpatients with AECB/AECOPD who received treatment for their exacerbation with the antibiotic moxifloxacin. Factors analyzed for late recovery included patient demographic characteristics, geographic region and disease severity. Additionally, logistic regression analysis was undertaken to identify factors associated with late recovery.
Results: The analysis population was 40,435 patients aged ≥35 years, from Asia-Pacific, Europe, the Americas and Middle East/Africa. Most were male (63.1%), mean age 60.4 years and current or ex-smokers (60.6%) with history of ≥2 exacerbations in the previous year. Patients who underwent spirometry ($n = 6408$, 19.7%) had moderate airflow obstruction (mean FEV_1 1.7 L). Both clinicians and patients reported that moxifloxacin provided clinical improvement in a mean of 3 days and recovery in 6 days. Clinical factors significantly associated with late recovery were: age ≥65 years, duration of chronic bronchitis >10 years, cardiac comorbidity, >3 exacerbations in the previous 12 months, current exacerbation type (Anthonisen I/II) and hospitalization in the last 12 months.

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Conclusions: In a large cohort of patients, all treated with the same antibiotic for an exacerbation of chronic bronchitis or COPD, the main factors associated with late recovery (≥8 days) were: older age, history of frequent exacerbations, current exacerbation type of Anthonisen I/II, history of prior hospitalizations and cardiac comorbid conditions.

Introduction

Chronic bronchitis and chronic obstructive pulmonary disease (COPD) together comprise a large and increasing health and economic burden,[1] with acute exacerbations of these diseases contributing significantly to the burden and progression of disease.[2–4] COPD is projected to become the third most frequent cause of death worldwide by the year 2030,[1] and ranks fifth in terms of the global burden of disease.[4] Despite the major impact of these conditions on patients and healthcare systems, relatively little is known of the epidemiology of exacerbations of COPD (AECOPD) or chronic bronchitis (AECB); large-scale epidemiological studies of patients experiencing acute exacerbations are rare.

Important treatment goals for AECB/AECOPD are to reduce the duration of an exacerbation and to increase the time to the next exacerbation. Factors affecting long- and short-term clinical outcomes in patients with AECB/AECOPD have been examined previously by Wilson et al.[5] Clinical cure was positively influenced by antibiotic treatment choice; higher cure rates were seen for moxifloxacin than comparator (amoxicillin, clarithromycin, cefuroxime)-treated patients, while cardiopulmonary disease, forced expiratory volume in 1 s (FEV_1) <50% predicted and ≥4 exacerbations in the previous year were indicative of a poorer treatment outcome.

The Greatest International ANtibiotic Trial (GIANT) trial provides data from a large observational cohort of patients who were all treated with the same antibiotic (moxifloxacin). As antibiotic treatment itself influences treatment outcome, using a single antibiotic should eliminate potential bias due to the type of antibiotic used.

Results from more than 9200 patients in the European regions of the GIANT study[6] and 11,377 patients from China[7] have been reported previously. This manuscript is the report of the full data set from the GIANT study (gathered across 46 countries over 4 years).

The GIANT study provided a large database that has been used to assess the risk factors for delayed recovery from an exacerbation in a real-life situation outside the regimented environment of a clinical trial. To standardize one potential variable, all patients received the same antibiotic treatment. Knowledge of factors that predispose patients to early or late recovery (≥8 days) may help to guide clinicians in their treatment choices, their advice to patients, and will have an impact on the future design of clinical studies.

Methods

Study design

GIANT was a prospective, multicenter, observational, non-interventional study that collected data on the epidemiology and outcomes of patients with AECB between February 2004 and November 2007. The study was conducted in Asia-Pacific, Europe, the Americas, and the Middle East/Africa (see Supplementary Material for a full list of participating countries). A standard protocol was used and all doctor and patient documentation was translated into appropriate languages. Patients were treated with moxifloxacin in accordance with local labeling, guidelines and ethical approval rules in participating countries.

Patients

Patients were enrolled in the study if they were suffering from an AECB/AECOPD and their clinician determined that they should receive treatment with an antibiotic. All patients were treated with open label, oral moxifloxacin, 400 mg once a day for 5–10 days. All clinical decisions about selection and implementation of individual medical treatment and diagnostic measurements were made by the participating clinicians. The populations analyzed in the GIANT study are shown in Fig. 1. For the overall analysis of patient characteristics and the subanalyses by type of exacerbation and time to recovery, only patients aged ≥35 years were included. The lower age limit of 35 years was chosen to exclude those patients most likely to have had acute bronchitis and/or asthma rather than AECB/AECOPD.

Exacerbation definition and severity

The occurrence of an exacerbation was diagnosed based on the patient experiencing an acute increase in one or more of the respiratory symptoms of dyspnea, sputum volume and sputum purulence. These are the three clinical symptoms described by Anthonisen et al.[8] Patients were classified according to their symptoms as: type I exacerbations were those with all three symptoms, type II exacerbations were those with any two of the three symptoms and type III exacerbations were those in which any one of these symptoms was present. Recovery was assessed by the clinician and was defined as a cure, resulting in the patient being free of the symptoms of an acute exacerbation.

Study procedures

For each patient enrolled, baseline data on patient demographic and clinical characteristics were recorded. These included age, gender, body mass index (BMI), smoking status, employment status, duration of chronic bronchitis, number of exacerbations in the previous year, clinician visits and hospitalizations in the previous year, FEV_1, concomitant diseases (including COPD), symptoms of the current exacerbation according to Anthonisen criteria,[8] severity of the current exacerbation (as assessed by the

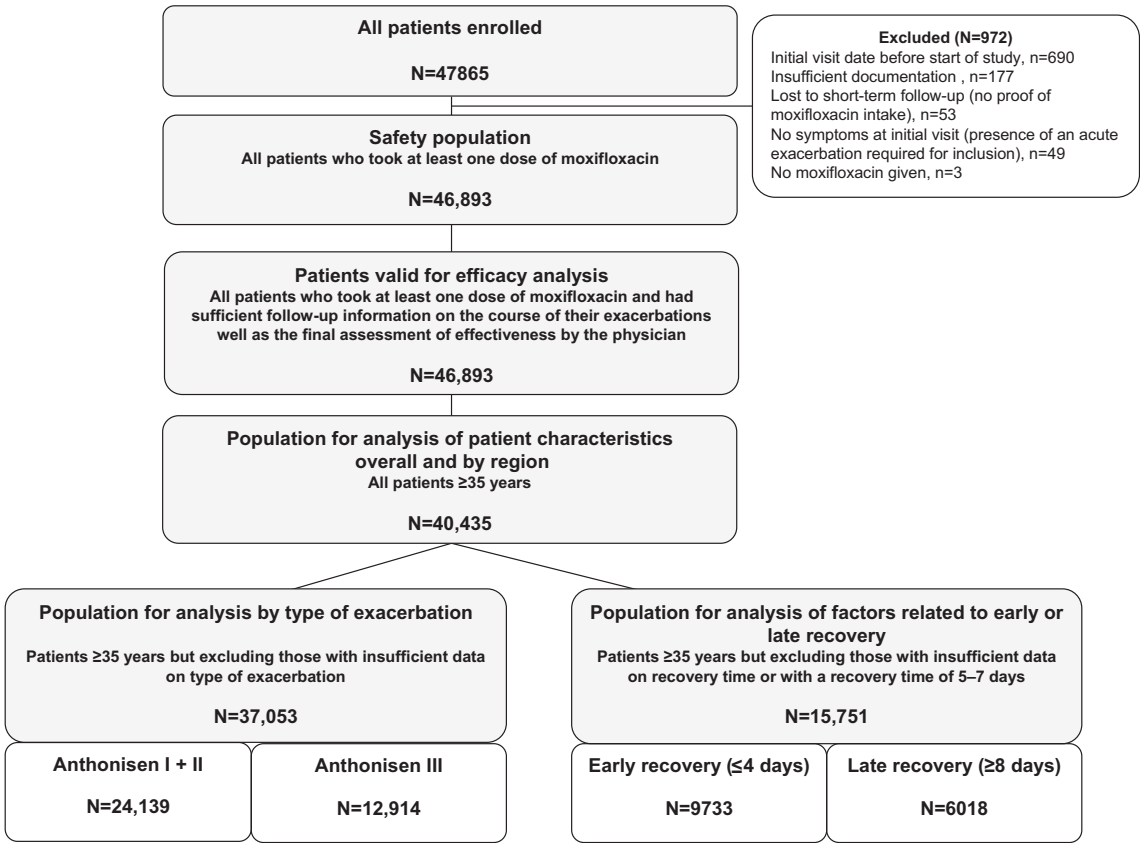

Figure 1 Disposition of patients in the various analysis populations of the GIANT study.

clinician), disruptions to daily life caused by the previous exacerbation (effects on daily activities and on sleep patterns as assessed by the patient), previous treatment for exacerbations and concomitant medication.

The study period covered the course of moxifloxacin treatment. There was no formal schedule of visits. Patients were seen as often as necessary in line with routine practice in that region (generally one or two follow-up visits). The clinician made an assessment of time to improvement in symptoms and time to recovery. At each follow-up visit, the patient's symptoms, changes in concomitant medication and any adverse events were recorded using standard adverse event report forms attached to the case report form. At the final follow-up visit, an overall assessment of treatment was made.

Study analyses

Descriptive analyses of the data were performed using summary statistics for categorical and quantitative data. Patient demographic and clinical characteristics were analyzed according to region (Asia-Pacific, Europe, the Americas and Middle East/Africa), exacerbation symptom criteria (Anthonisen I plus II vs Anthonisen III) and time to recovery in days. Patients were categorized into tertiles based on recovery time: $\leq$4 days (early-recovery group), 5—7 days, or $\geq$8 days (late-recovery group), according to previously published results on time to recovery.[9,10] This distribution resulted in three subgroups containing similar numbers of patients. Patients who recovered most quickly (early-recovery group) were statistically compared with those who had the most prolonged recovery (late-recovery group) to maximize the likelihood of observing significant differences, thus providing clear characterization of the patients at risk of late recovery, which is the main objective of the analysis.

Simultaneous comparisons were carried out using multifactorial test statistics (analysis of variance [ANOVA], Pearson's χ^2 test). Differences between subgroups of patients were analyzed using the Wilcoxon rank sum test. A multivariate analysis was also carried out using a backward selection model, in which clinical and demographic factors were entered initially and then terms that were not significant ($P \geq 0.05$) were excluded. The factors included were gender (male vs female), geographic area (each region vs others), age ($\geq$65 vs $<$65 years), BMI ($<$20 vs $\geq$20 kg/m^2), duration of chronic bronchitis ($<$10 years vs $\geq$10 years), current smoking history (yes vs no), cardiac comorbidity (yes vs no), FEV_1 assessed at baseline (yes vs no), exacerbations in the previous 12 months ($\geq$3 vs $<$3), hospitalization in the previous 12 months (yes vs no) and severity of exacerbation based on Anthonisen criteria (I + II vs III).

Results

Patient populations

The safety population consisted of 46,893 patients who received at least one dose of moxifloxacin (Fig. 1). The

population used for analysis of patient characteristics comprised 40,435 patients aged ≥35 years. These patients were included in the overall analysis of baseline demographics and clinical characteristics, and the analysis by region (Asia-Pacific: $n = 25,074$, Europe: $n = 10,164$, the Americas: $n = 2487$, and Middle East/Africa: $n = 2710$). Of the 40,435 patients 52.0% had a concomitant diagnosis of COPD (Table 1).

The patient populations for the exacerbation type and time-to-recovery analyses were drawn from the primary population aged ≥35 years old (Fig. 1). Of 37,053 patients valid for analysis of exacerbation type, 24,139 had Anthonisen type I or II and 12,914 had Anthonisen type III. There were 15,751 patients valid for the analysis of recovery time: 9733 were in the early-recovery group (≤4 days) and 6018 in the late-recovery group (≥8 days). Of these, 11,486 patients had a full data set available for statistical analysis, 6649 in the early-recovery group and 4837 in the late-recovery group.

Baseline demographics and clinical characteristics

The baseline demographics and clinical characteristics of the population used for analysis are shown in Table 1. Most patients were male (63.1%), mean age 60.4 years, current or ex-smokers (60.6%) with a history of at least two exacerbations in the previous year. FEV_1 assessments were available for 6408 (19.7%) patients in the population and demonstrated moderate airflow obstruction with a mean FEV_1 of 1.7 L. Nearly two-thirds of the patients were suffering from an Anthonisen type I or II exacerbation.

There were variations in patient profiles across the different regions, particularly in terms of smoking status, duration of chronic bronchitis, disease severity and the presence of comorbid cardiac disease, diabetes and other lung disease (Table 1).

Systemic corticosteroids were given alone or in combination with inhaled corticosteroids in 9% of the study cohort. Patients with more severe symptoms were more likely to receive corticosteroids. There were no differences in patients' outcomes as compared to patients that did not receive corticosteroids.

Patient demographic and clinical characteristics according to type of exacerbation

Demographic and clinical characteristics were assessed by the severity of the exacerbation (Anthonisen criteria). Table 2 shows the characteristics of these patients.

Compared with patients in the Anthonisen Type III group, patients in the Anthonisen I plus II group were more likely to be male, aged >60 years, to be a current or ex-smoker and to have had chronic bronchitis for more than 10 years. In the last 12 months they were likely to have had more exacerbations, more physician visits and more hospitalizations than those with a type III Anthonisen exacerbation. For the current exacerbation, they were more likely to have disturbance to daily activities and to have disturbed sleep. Patients in the Anthonisen I plus II group were also most likely to have associated comorbid conditions, such as an underlying lung disease.

Clinician- and patient-reported outcomes of treatment with moxifloxacin

According to assessment by the treating clinician, the mean time to clinical improvement after initiation of treatment with moxifloxacin was 3.3 days. Time to improvement was shortest in patients with Anthonisen class III. The clinician-assessed mean time to recovery was 5.8 days.

Patient demographic and clinical characteristics according to recovery time

Demographic characteristics of patients with early (≤4 days) vs late (≥8 days) recovery are shown in Table 3. In both Europe and the Americas a higher proportion of patients had late recovery. Patients in the late-recovery group had a more serious disease profile than those in the early-recovery group. Those with late recovery were older (mean age of 63.8 years, 48.4% aged over 65 years vs mean age 58.4 years; 32.0% aged ≥65 years), more likely to have suffered from chronic bronchitis for >10 years, with more exacerbation episodes overall in the past 12 months and a greater likelihood of having >3 exacerbations in 12 months. A higher percentage of patients in the late-recovery group were assessed by spirometry than in the early-recovery group. The current exacerbation was more severe in the late than in the early-recovery group; 72.3% of patients were classed as Anthonisen class I or II in the late-recovery group vs 49.8% in the early-recovery group. Cardiac comorbidities were documented almost twice as often in the late- (36.2%) vs the early- (19.9%) recovery group and there was a slightly higher rate of hospitalization in the late-recovery group.

Results of the multivariate logistic regression analysis of risk factors for late recovery are shown in Table 4. Clinical and patient-related factors most strongly associated with late recovery were age ≥65 years, duration of chronic bronchitis >10 years, presence of cardiac comorbidity, having >3 exacerbations in the previous 12 months, having a current exacerbation as Anthonisen type I or II, and being hospitalized in the last 12 months. Patients assessed by spirometry were also more likely to be in the late-recovery group.

Safety and tolerability

Adverse events were recorded for 1.8% of patients in the safety population (847/46,893) during the treatment period. They led to permanent discontinuation of therapy in 0.3% of patients (155/46,893). Adverse drug reactions (ADRs) occurred in 1.2% (557/46,893) of patients. The predominant ADRs were gastrointestinal ($n = 353/46,893$ patients; 0.8%): nausea (139 [0.3%] patients), diarrhea (93 [0.2%] patients) and vomiting (57 [0.1%] patients). Of the 46,893 patients, 0.2% (96) had at least one serious adverse event. Serious adverse events with fatal outcome were reported in 46 (0.1%) patients; only one death was associated with therapy. This patient with a history of COPD developed concomitant pulmonary embolism in the context of sepsis and renal insufficiency.

Table 1 Patient demographic and clinical characteristics of the patient population aged ≥35 years.

	Total (N = 40,435)	Asia-Pacific (N = 25,074)	Europe (N = 10,164)	Americas (N = 2487)	Middle East/ Africa (N = 2710)	P-value[a]
Investigator specialty, %[b]						<0.0001[c]
Family clinician	20.7	11.3	51.2	1.5	10.8	
Chest clinician	65.1	79.0	38.4	60.8	41.1	
Male sex, %	63.1	66.6	55.9	50.5	69.7	<0.0001[c]
Age (years), mean (SD)	60.4 (13.1)	60.0 (13.2)	62.2 (12.6)	64.6 (12.7)	53.3 (11.3)	<0.0001[d]
BMI (kg/m^2), mean (SD)	24.7 (4.6)	23.3 (3.9)	26.8 (4.5)	26.4 (5.0)	27.7 (5.1)	<0.0001[d]
Smoking status, %						<0.0001[c]
Current smokers	29.7	28.6	30.2	25.0	42.1	
Ex-smokers	30.9	30.8	30.8	42.7	21.5	
Never smoked	38.0	40.0	37.2	29.9	30.7	
In employment, %	40.3	43.0	33.8	31.2	47.7	<0.0001[c]
Chronic bronchitis for >10 years, %	19.3	15.6	29.9	21.0	12.7	<0.0001[c]
FEV_1 (L), mean (SD)	1.7 (0.8)	1.6 (0.8)	1.8 (0.8)	1.5 (0.7)	1.8 (0.9)	<0.0001[d]
Patients assessed by spirometry, n (%)	6408 (19.7)[e]	1803 (10.5)[e]	(3533 34.8)	704 (28.3)	368 (13.6)	
Events in the past 12 months, mean (SD)						
Number of exacerbations	2.4 (2.2)	2.5 (2.3)	2.2 (1.9)	2.4 (2.0)	3.0 (2.6)	<0.0001[c]
Clinician visits	3.2 (3.1)	2.7 (2.6)	4.5 (4.1)	3.0 (2.6)	3.1 (2.7)	<0.0001[c]
Hospitalizations	0.6 (1.1)	0.8 (1.1)	0.3 (0.8)	0.5 (1.1)	0.4 (1.1)	<0.0001[c]
Disruptions during previous exacerbations, mean (SD)						
Days daily activities affected	5.3 (5.8)	4.4 (5.2)	7.7 (6.6)	5.9 (7.0)	4.7 (4.9)	<0.0001[c]
Nights with sleep disturbance	3.5 (4.5)	2.9 (3.8)	4.8 (5.5)	3.9 (5.5)	3.5 (4.2)	<0.0001[c]
Characterization of current exacerbation according to Anthonisen criteria, %						<0.0001[b]
Anthonisen type I	26.3	19.5	38.9	32.6	36.4	
Anthonisen type II	33.4	33.1	34.5	31.7	33.1	
Anthonisen type III	31.9	36.5	23.0	30.3	25.1	
Severity of current exacerbation according to investigator's judgment, %						<0.0001[b]
Mild	16.4	20.4	8.1	16.3	10.3	
Moderate	63.8	65.0	62.5	62.4	58.3	
Severe	19.5	14.2	29.1	20.7	30.6	
Comorbid conditions, %[f]						
None	18.6	20.7	14.0	13.3	21.1	
Cardiac disease(s)	25.1	23.6	32.3	23.8	13.7	
Diabetes	13.6	12.3	14.8	14.2	19.7	
Lung disease(s)	71.1	67.6	78.3	77.8	70.1	
COPD	52.0	46.4	63.1	66.4	49.9	

Aggregate percentages vary and are less than 100 due to missing values.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
Anthonisen type I: increased dyspnea, sputum volume, and sputum purulence present; Anthonisen type II: two of increased dyspnea, sputum volume, or sputum purulence present; Anthonisen type III: one of increased dyspnea, sputum volume, or sputum purulence present.

[a] Europe was used as the reference group; each region was tested against Europe, not against the other regions.

[b] Chest clinicians include pulmonologists and internal medicine specialists; the numbers of investigators in other clinical specialties are not shown.

[c] χ^2 test.

[d] ANOVA.

[e] FEV_1 was not documented in the Philippines so the percentages in this table for the total population and for Asia-Pacific were calculated without 7862 patients from Philippines; this makes the percentage of patients in Asia-Pacific with an FEV_1 assessment artificially low.

[f] Patients may have more than one comorbid condition.

Table 2 Patient characteristics according to severity of the exacerbation (Anthonisen type I plus type II vs Anthonisen type III) in the population of 37,053 patients aged ≥35 years who were valid for inclusion in the severity analysis.

Characteristic	Anthonisen I plus II (N = 24,139)	Anthonisen III (N = 12,914)	P-value
Male sex, n (%)	15,605 (64.6)	7966 (61.7)	<0.001[a]
Age (years), mean (SD)	61.7 (12.7)	59.0 (13.3)	<0.001[b]
BMI (kg/m^2), mean (SD)	24.9 (4.6)	24.4 (4.4)	<0.001[b]
Smoking status, n (%)			<0.001[a]
Current and ex-smokers	15,733 (65.2)	7190 (55.7)	
Never smoked	8096 (33.5)	5538 (42.9)	
In employment, n (%)	8822 (36.5)	5802 (44.9)	<0.001[a]
Chronic bronchitis for >10 years, n (%)	5815 (24.1)	1759 (13.6)	<0.001[a]
FEV_1 (L) in patients assessed, mean (SD)[c]	1.7 (0.8) (n = 4873)	1.8 (0.8) (n = 1374)	<0.001[b]
Events in the past 12 months, mean (SD)			
Exacerbations	2.7 (2.3)	2.2 (2.1)	<0.001[b]
Clinician visits	3.5 (3.3)	2.7 (2.7)	<0.001[b]
Hospitalizations	0.7 (1.1)	0.5 (1.0)	<0.001[b]
Previous exacerbation, mean (SD)			
Days with daily activities affected	6.2 (6.1)	4.2 (5.3)	<0.001[b]
Nights with sleep disturbances	4.1 (4.8)	2.7 (3.9)	<0.001[b]
Comorbid conditions, n (%)[d]			
Lung disease(s)	18,844 (78.1)	8166 (63.2)	<0.001[a]
Other	3319 (13.7)	2966 (23.0)	<0.001[a]

Aggregate percentages vary and are less than 100 due to missing values.
BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
Anthonisen type I: increased dyspnea, sputum volume, and sputum purulence present; Anthonisen type II: two of increased dyspnea, sputum volume, or sputum purulence present; Anthonisen type III: one of increased dyspnea, sputum volume, or sputum purulence present and includes patients with one cardinal Anthonisen symptom and those with one cardinal symptom plus one or more minor symptoms.
[a] χ^2 test.
[b] Wilcoxon rank sum test.
[c] FEV_1 was not documented in the Philippines.
[d] Patients may have more than one comorbid condition.

Discussion

The GIANT study is the largest global investigation conducted to date into the course and impact of episodes of AECB/AECOPD in outpatients across Asia-Pacific, Europe, the Americas, and the Middle East/Africa. The demographic and clinical data collected from the large database of 46,893 patients allowed the development of demographic and clinical profiles of a 'typical' patient with AECB/AECOPD as well as profiles of specific patient subgroups, such as those with different severities of exacerbation (Anthonisen I or II vs Anthonisen III) or demonstrating early (≤4 days) or late (≥8 days) recovery. The overall finding of the GIANT study is that in patients who are all treated with the same antibiotic, baseline patient demographic and clinical characteristics have a major impact on the subsequent outcomes of treatment for AECB/AECOPD.

A number of studies have described that patient-related factors are important determinants of treatment outcome.[11–17] A computer-based general practice study by Ball et al. found that a history of cardiopulmonary disease and >4 exacerbations in the past 12 months were risk factors for re-presenting with a further chest infection.[11] In a retrospective chart analysis of patients treated with a range of first-line antimicrobials, risk factors associated with treatment failure were: FEV_1 <35%, use of home oxygen, >3 exacerbations in the previous year, a history of previous pneumonia or sinusitis and use of maintenance corticosteroids. However, age, comorbidity and the choice of antibiotic were not found to be risk factors.[12] Data from Spain indicated that FEV_1 impairment, chronic mucus hypersecretion and increasing age were associated with the risk of frequent exacerbations.[13] Another Spanish study, using data from general practice,[14] identified ischemic heart disease, the degree of dyspnea and the number of visits to the general practitioner in the previous year as strongly and independently associated with treatment relapse. However, the severity of exacerbation was not found to be associated with the relapse rate. Thus, these studies have shown that one or more of the following variables are risk factors for poor short-term outcomes: age, severe airway disease, comorbid cardiopulmonary disease, prolonged chronic bronchitis or a high frequency of exacerbations. However, these studies all included much smaller numbers of patients than GIANT, included patients treated with a range of antimicrobials, assessed only a limited number of patient-related factors or were specific to one region or country.

Table 3 Characteristics of patients in the groups with early recovery from an exacerbation (≤4 days) or late recovery from an exacerbation (≥8 days) in 15,751 patients aged ≥35 years who were valid for the analysis of recovery time.

Characteristics	Early recovery (≤4 days) (N = 9733)[a]	Late recovery (≥8 days) (N = 6018)[a]	P-value
Recovery time (days), mean (SD)	3.1 (0.9)	10.2 (2.5)	<0.0001[c]
Investigators specialty, %			<0.0001[d]
Family physician	23.3	24.8	
Chest physician	62.2	62.3	
Other	7.3	6.0	
Missing	7.3	7.0	
Gender, %			0.6659[d]
Male	62.4	62.9	
Female	36.2	36.0	
Missing	1.3	1.1	
Age, mean (SD)	58.4 (13.2)	63.8 (12.5)	<0.0001[d]
≥65 years, %	32.0	48.4	<0.0001[d]
Geographic area, %			<0.0001[d]
Asia-Pacific	67.4	45.4	
Europe	19.0	41.4	
The Americas	5.4	7.3	
Middle East/Africa	8.2	5.8	
BMI (kg/m^2), mean (SD)	24.7 (4.7)	25.2 (4.8)	<0.0001[c]
Chronic bronchitis, %			<0.0001[d]
≤10 years	85.9	65.9	
>10 years	11.3	31.7	
Missing	2.8	2.4	
Smoking status, %			<0.0001[d]
Current	31.1	28.2	
Non-smoker or ex-smoker	67.5	70.5	
Missing	1.4	1.3	
Presence of cardiac comorbidity, %	19.9	36.2	<0.0001[d]
FEV_1 (L), mean (SD)[b]	1.8 (0.9)	1.7 (0.8)	<0.0001[c]
Patients assessed, %	16.8	26.5	
Exacerbations in last 12 months, mean (SD)	2.3 (2.2)	2.8 (2.3)	<0.0001[c]
≤3, %	64.2	62.4	<0.0001[d]
>3, %	18.3	25.7	
Missing, %	17.5	11.9	
Hospitalizations in last 12 months, mean (SD)	0.6 (1.0)	0.7 (1.1)	<0.0001[c]
Yes, %	29.3	38.1	<0.0001[d]
Current exacerbation symptoms, %			<0.0001[d]
Anthonisen type I and II	49.8	72.3	
Anthonisen type III	37.9	23.3	
Missing	12.4	4.4	

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
[a] Full data for all observations were available for 11,486 patients, 4265 patients were excluded from the various analyses due to missing values; missing values are displayed in the table where appropriate.
[b] FEV_1 was not documented in the Philippines so data from patients in the Philippines are not included in percentage calculations.
[c] Wilcoxon rank sum test.
[d] χ^2 test.

The GIANT study is the first large prospective non-interventional observational study to investigate a wide range of potential risk factors for late recovery from a treated exacerbation. A logistic regression analysis showed that in this non-interventional study population there were seven key risk factors for late recovery from an exacerbation: age ≥65 years, duration of chronic bronchitis >10 years, presence of a cardiac comorbidity, multiple exacerbations (>3) in the previous 12 months, current exacerbation classified as Anthonisen I or II, hospitalization in the last 12 months and spirometry assessment. Smoking history had no effect on the time to recovery — a finding supported by the MOSAIC study[5] in which current smoking history had no effect on short-term clinical outcomes. Clear definition of the patient profile associated with late recovery may allow clinicians to identify patients at highest risk of poor outcome, to choose the most appropriate antimicrobial treatment and to plan their patient management accordingly.

Table 4 Factors associated with late recovery (≥8 days) from an exacerbation in 11,486 patients aged ≥35 years (early recovery, $n = 6649$; late recovery, $n = 4837$) with a full data set available for all factors in the analysis.

Factor	Odds ratio point estimate	95% CI	*P*-value‡
Region			
Europe vs rest of world	2.589	2.343—2.861	<0.0001
Americas vs rest of world	1.756	1.495—2.062	<0.0001
Age			
≥65 years vs ≥35—<65 years	1.233	1.130—1.345	<0.0001
Duration of chronic bronchitis			
>10 years vs ≤10 years	2.262	2.041—2.506	<0.0001
Cardiac comorbidity			
Yes vs no	1.559	1.421—1.711	<0.0001
Assessment of FEV_1			
Yes vs no	1.368	1.223—1.530	<0.0001
Number of exacerbations in last 12 months			
>3 vs ≤3	1.147	1.044—1.260	0.0034
Anthonisen score			
Anthonisen type I plus II vs Anthonisen type III	1.799	1.646—1.965	<0.0001
Hospitalization in last 12 months			
Yes vs no	1.456	1.329—1.594	<0.0001

FEV_1, forced expiratory volume in 1 s.
‡χ^2 test.

The GIANT study has also highlighted that additional clinician education may be required on the use of spirometry. Despite guidelines recommending the use of spirometry[18—20] for the diagnosis or follow-up of COPD, in patients with AECB/AECOPD spirometry is not performed routinely in primary care[21—24] even in regions with ready access to equipment. The data presented here show that FEV_1 was measured in only about 20% of patients. The spirometric data indicate that many of the patients in the GIANT study had moderate airway obstruction, and having used spirometry was significantly associated with late recovery. This may be because many clinicians tended to order the assessment only for more severely ill patients or those with complications. The GIANT study also demonstrates that across the world, clinicians are initiating antibiotic treatment in patients with Anthonisen III exacerbations. However, for an exacerbation to be considered of probable bacterial origin it must be associated with two or more Anthonisen criteria or even better, with a change in sputum color[25]; current guidelines[26,27] state that an exacerbation which is unlikely to be of bacterial origin (i.e. Anthonisen III) should not be treated with antibiotics.

Finally, in the GIANT study, where diagnosis and management of an exacerbation reflected 'real-life' routine clinical practice, treatment with moxifloxacin was effective and well tolerated both according to the clinician and the patient. Patients felt better and were able to resume their daily lives and clinicians reported clinical improvement and recovery rates within 3—7 days. This is in line with clinical response rates and adverse-event profiles reported for moxifloxacin in clinical trials[11,28,29] and supports current recommendations that moxifloxacin is suitable as (i) a first-line treatment option for patients presenting with multiple risk factors for poor outcome, (such as severe impairment of lung function, comorbid disease(s), or frequent exacerbations),[5] or (ii) as a second-line treatment option for patients who experience initial treatment failure.[29]

Limitations of the study

As the GIANT study was a non-randomized study, no control group comparisons could be made between moxifloxacin and placebo or another active treatment. However, as the intention of the study was to gather baseline and on-treatment data, such a comparison with another treatment was never intended. Also, its non-interventional design resulted in a less rigid follow up than seen in randomized controlled trials. The GIANT study provides data on over 40,000 patients, and gives a useful global picture when viewed within the constraints of an observational study.

Another difference between an observational study and a randomized, controlled trial is that the threshold for reporting adverse events either from the patient to the clinician or from the clinician can vary because it is not possible to closely monitor safety in such a large population. However, the study did not reveal any unexpected serious ADRs, so the study supports the established safety profile of moxifloxacin.[29]

Other possible limitations include the fact that the GIANT protocol relied on patient recall rather than clinical records to obtain the exacerbation history and that some assessments were based on the investigators' judgment alone (e.g. time to improvement, time to cure and Anthonisen grade). However, recent studies have shown that patient history of previous exacerbations accurately reflects future events.[30,31]

Finally, it is possible that the percentage of patients with a recording of FEV_1 could be an underestimate, as in some instances it is possible that the investigator recording the study data did not know, or did not remember whether this had been done.

Conclusions

Marked differences were seen across regions in the characteristics of patients presenting with AECB/AECOPD. Late recovery from AECB/AECOPD in patients treated with an appropriate antimicrobial is more likely to occur in older patients, those with a longer duration of chronic bronchitis or COPD, more severe disease, cardiac comorbidity, or a history of >3 exacerbations per year. Clinical studies should be designed to take these risk factors into consideration.

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Conflict of interest statement

Stephanie Heldner and Kathrin Stauch are employees of Bayer Schering Pharma.

Antonio Anzueto has participated as a speaker in scientific meetings or courses organized and financed by pharmaceutical companies including: Boehringer Ingelheim, Bayer Schering Pharma, Pfizer, GlaxoSmithKline, and the Schering Plough Corporation. He has also provided consultancy services to Boehringer Ingelheim, Bayer Schering Pharma, Pfizer, GlaxoSmithKline and the Schering Plough Corporation. He has been the principal investigator for research grants and the University of Texas Health Science Center at San Antonio was paid for participating in multicenter clinical trials sponsored by: C R Bard, Lilly, GSK, Pfizer, and the National Institutes of Health, National Heart, Lung and Blood Institute.

Marc Miravitlles has participated as a speaker in scientific meetings or courses organized and financed by pharmaceutical companies including: Boehringer Ingelheim, Bayer Schering Pharma, Pfizer, Novartis, and AstraZeneca. He has been a consultant for Boehringer Ingelheim, Bayer Schering Pharma, Pfizer, AstraZeneca and Novartis.

Santiago Ewig has participated as a speaker in scientific meetings or courses organized and financed by pharmaceutical companies including: GlaxoSmithKline, Boehringer Ingelheim, Bayer Schering Pharma, Pfizer, Wyeth, Novartis, AstraZeneca and MSD.

Delfino Legnani has participated as a speaker in scientific meetings or courses organized and financed by pharmaceutical companies including Bayer Schering Pharma, Sanofi Aventis and GSK.

Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rmed.2012.06.002.

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