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Five day moxifloxacin therapy compared with 7 day clarithromycin therapy for the treatment of acute exacerbations of chronic bronchitis

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In this multinational, randomized, double-blind study, the efficacy and safety of a 5 day course of moxifloxacin 400 mg orally od was compared with that of a 7 day course of clarithromycin 500 mg orally bd in 750 patients with acute exacerbations of chronic bronchitis, characterized by at least two of the symptoms: sputum purulence, increased sputum volume or increased dyspnoea. Seven days after the end of therapy, clinical cure was achieved for 89% (287 of 322) of efficacy-evaluable patients in the moxifloxacin group and 88% (289 of 327) of patients in the clarithromycin group (95% CI, –3.9%, 5.8%). At follow-up (21–28 days post-treatment), the continued clinical cure rates were 89% (256 of 287) for moxifloxacin and 89% (257 of 289) for clarithromycin. A total of 342 pathogenic bacteria were isolated from the sputum of 287 patients. The most common pathogens were *Haemophilus influenzae* (37%), *Streptococcus pneumoniae* (31%) and *Moraxella catarrhalis* (18%). Seven days post-treatment, a successful bacteriological response was obtained for 77% (89 of 115) of patients in the moxifloxacin group and 62% (71 of 114) of patients in the clarithromycin group, indicating superiority of moxifloxacin (95% CI, 3.6%, 26.9%). Both treatments were well tolerated with few adverse events. This study demonstrated that for the treatment of acute exacerbations of chronic bronchitis a 5 day course of moxifloxacin 400 mg od was clinically equivalent and bacteriologically superior to a 7 day course of clarithromycin 500 mg bd.

Introduction

Chronic bronchitis is a clinical diagnosis in patients presenting with persistent cough and excessive secretion of mucus on most days for at least three consecutive months in two consecutive years.[1] Patients presenting clinical symptoms of chronic bronchitis are a heterogeneous group with regard to the severity of their condition. Airflow obstruction is present to a variable degree, and emphysema may or may not be present.[2] Acute exacerbations of chronic bronchitis (AECB) occur, but their cause can be difficult to identify and may include air pollutants, allergens and viruses as well as bacterial pathogens. Despite some geographical variation in the prevalence of specific bacterial types, the bacterial species isolated most frequently from the sputum of patients with AECB are remarkably similar worldwide and include non-typable *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*.[3] A number of clinical investigations have demonstrated the efficacy of antibiotics in AECB, especially in patients with at least two of the three symptoms of increased dyspnoea, increased sputum volume and sputum

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purulence,[4] and with more severe airflow obstruction.[5] The causative pathogen is only rarely identified in clinical practice, and therefore, since treatment is usually empirical, it needs to cover the most likely pathogens.

Increased bacterial resistance has caused concern regarding the efficacies of currently available antibiotic therapies. Up to 35% of *H. influenzae* and >90% of *M. catarrhalis* produce β-lactamases.[6,7] The prevalence of penicillin-resistant strains of *S. pneumoniae* reported worldwide ranges from 1 to 59%.[8] In Europe there is considerable national, regional and local variation in the figures for penicillin-resistant pneumococci. Prevalence rates of up to 40% have been reported in Spain[9] and 58% in Hungary,[10] although in other countries such as Germany or the UK the prevalence rates are <5%.[11,12] However, a recent report suggests that the prevalence in the UK is also increasing.[13] An analysis conducted in 30 hospitals from various parts of the USA revealed that the rate of penicillin-resistant *S. pneumoniae* ranged from 4% in New York to 48% in Georgia.[14] Penicillin resistance can be associated with resistance to other commonly prescribed antibiotics, particularly the macrolides. A recent survey from the UK showed that 9% of pneumococci demonstrated in-vitro resistance to clarithromycin,[12] a doubling compared with figures obtained in a survey 1 year earlier.[15]

Moxifloxacin (formerly BAY 12-8039) is a novel 8-methoxyquinolone with excellent activity against a wide range of microorganisms associated with community-acquired respiratory tract infections. In comparison with older quinolones, moxifloxacin has retained high activity against Gram-negative pathogens but displays significantly improved activity against atypicals, Gram-positive and anaerobic organisms.[16–18] Against *S. pneumoniae*, the MIC_{90} of moxifloxacin is 0.12–0.25 mg/L; there is no difference between penicillin-susceptible and penicillin-resistant strains.[19,20] Single and multiple dose pharmacokinetic studies confirmed that the pharmacokinetic profile of moxifloxacin allows od oral dosing (average terminal half-life, 13 h), and there was excellent penetration into the bronchial mucosa.[21,22]

The current study was designed to compare efficacy and safety of a 5 day course of moxifloxacin 400 mg od with that of a 7 day course of clarithromycin 500 mg bd, for the treatment of patients suffering from AECB.

Materials and methods

Trial setting

This was a multinational, prospective, randomized, double-blind, two-armed controlled clinical trial conducted at 85 outpatient or hospital centres in eight European countries: Austria, France, Germany, Greece, Netherlands, Spain, Switzerland and the UK. Appropriate ethics committee approval was obtained at each centre.

Patient selection

Adult patients aged 18 years or above with underlying chronic bronchitis as defined by a cough productive of sputum for at least three consecutive months, for more than two consecutive years, were eligible for enrolment into the trial if they suffered from an acute exacerbation of their condition, clinically thought to be caused by a bacterial pathogen. Patients had to present with at least two of the following three symptoms: purulent or mucopurulent sputum, increased sputum volume and increased dyspnoea, i.e. a type 1 or type 2 exacerbation as described by Anthonisen *et al*.[4] Written informed consent was obtained before patient enrolment. Patients were excluded from study participation because of known antibiotic allergy, pregnancy and lactation, significant renal or hepatic impairment, concomitant serious illness, recent antibiotic therapy and recent participation in another clinical trial.

Antibacterial therapy

Patients were randomized to receive one of two treatments: moxifloxacin 400 mg od for 5 days or clarithromycin 500 mg bd for 7 days. Moxifloxacin was provided by Bayer AG (Leverkusen, Germany) and clarithromycin was purchased from Abbott Laboratories (Chicago, IL, USA). In order to maintain the double-blind study design, the tablets administered were encapsulated and visually indistinguishable, and patients in the moxifloxacin arm received placebo capsules as appropriate, including placebo capsules on treatment days 6 and 7. The study drugs were taken without regard to meals, and at least 6 h after or 2 h before any dose of antacids.

Clinical assessments

Patients were evaluated before the first dose of study medication, at day 7 (i.e. at the end of the double-blinded study drug treatment), at day 14 and at days 28–35. At all visits, clinical assessments were made regarding the severity and/or frequency of the following AECB signs and symptoms and compared with baseline: cough, wheeze, dyspnoea, sputum quality and volume. The presence or absence of fever and auscultation findings was also recorded, and lung function measurements (FEV_1) were performed.

The clinical response of the patients was categorized as: (i) clinical cure (resolution of clinical signs and symptoms related to the AECB, not requiring any further antibiotic therapy); (ii) clinical improvement (improvement of signs and symptoms of AECB, not requiring any further antibiotic therapy), only applicable to day 7 assessment; (iii) clinical failure (failure to respond to the study drug, requiring a modification in antibiotic therapy or resulting in death from the primary diagnosis); (iv) clinical relapse (initial resolution or partial resolution of signs and symptoms of AECB, but subsequent recurrence of the condition,

requiring further antibiotic therapy), only applicable to day 14 and days 28–35 assessments; and (v) indeterminate (clinical evaluation not possible for any reason).

Bacteriological assessments

A sputum sample was obtained pre-treatment, if possible, and at any of the subsequent visits, and forwarded to a local or central laboratory (depending on the country) for culture within 24 h by a standardized protocol. Etest (AB Biodisk, Lund, Sweden) was used to determine the MIC for the causative organisms to moxifloxacin and clarithromycin. Bacteriological responses were assessed for patients who provided a bacteriologically positive pre-treatment sputum sample. Investigators were asked to judge whether any cultured bacterial organism was: (i) infecting, (ii) a colonizer, (iii) a contaminant and (iv) part of the normal flora. Only organisms classified as 'infecting' were considered causative organisms and taken into account for the bacteriological response analysis. The bacteriological response assessment was based on the following definitions: (i) eradication (original causative pathogen(s) not present after treatment); (ii) presumed eradication (because of clinical improvement, the patient was not able to produce sputum); (iii) persistence (re-isolation of one or more of the causative organisms); (iv) presumed persistence (patient was clinical failure, but unable to produce sputum); (v) recurrence (initial suppression of the causative organism with re-isolation of the same organism during the follow-up period); and (vi) indeterminate (microbiological evaluation not possible for any reason). If any new bacterial organisms were isolated, the patients were graded as follows: (i) superinfection (new pathogen isolated during treatment) and (ii) re-infection (eradication of the original causative pathogen(s) with subsequent isolation of one or more new pathogen(s)). In case of more than one pre-treatment causative organism, the bacteriological response by patient was calculated as the worst bacteriological outcome for each of the causative organisms.

All sputum samples with causative organisms were included in the evaluation of bacteriological response. This decision was based on an analysis that was performed before unblinding of the study results. This analysis demonstrated that the pre-therapy pathogen spectrum, and the clinical and bacteriological responses were very similar between patients with sputum samples containing >25 polymorphonuclear granulocytes (PMN) per $\times 100$ microscopic field, and in all patients with sputum samples irrespective of the PMN count (data not shown).

Safety assessments

At each assessment visit, adverse events were recorded with regard to type, severity, seriousness, relationship to study drug and outcome. At the pre-treatment visit and at day 7, clinical laboratory tests (chemistry, haematology and urinalysis) were performed on blood and urine samples. Any clinically significant abnormalities were followed up until normalized.

Statistical analysis

The primary aim of the study was to prove the hypothesis that moxifloxacin was not less effective than clarithromycin based on the clinical cure rate at the day 14 visit in the efficacy-evaluable population.

Based on a failure rate of 10% in the control group, an equivalence (clinically relevant) delta of 10%, $\alpha = 2.5\%$ (one-sided), $\beta = 10\%$, the sample size estimation yielded $n = 268$ valid patients in each treatment group, including a 15% addition for the multicentre design of the study. With an assumed validity rate of approximately 85% for the primary efficacy parameter, $n = 316$ patients in each treatment group were to be enrolled in the study, giving a total of 632 patients.

The efficacy analysis was performed on the efficacy-evaluable and intention-to-treat (ITT) populations. All determinations of evaluability were made before unblinding. For a course to be judged efficacy-evaluable, the following criteria were to be met: (i) full documentation of AECB; (ii) study drug had been administered for a minimum of 3 full days (in case of clinical failure, because a classification of failure after a shorter time could be considered too fast a judgement before the drug could exert its full effect) or 5 full days (in case of clinical success, because clinical success without an appropriate period of drug intake might be interpreted as spontaneous cure); (iii) no other systemic concomitant antibiotic had been given unless the patient was a treatment failure; (iv) compliance with $\geqslant 80\%$ of study medication related to the length of time that treatment was taken; (v) no protocol violations influencing efficacy; (vi) random code not broken; and (vii) no essential data missing. In addition, for patients to be considered microbiologically valid, at least one causative organism had to be identified in a pre-treatment culture, and an appropriate post-treatment bacteriological evaluation (i.e. positive or negative culture or no material to culture) had to be available.

In both efficacy analyses, centres were clustered by geographical region prospectively before unblinding of the study results. The calculation of the 95% confidence intervals (see below) was adjusted to these clusters of centres. Demographic and baseline characteristics were summarized by treatment group; the two treatment groups were compared univariately by two-way analyses of variance (treatment group and region as fixed factors) and by a Cochran–Mantel–Haenszel test.

For the primary efficacy variable, a two-sided 95% CI for the difference between the two clinical cure rates (moxifloxacin minus clarithromycin) was calculated with Mantel–Haenszel weighting. If the lower limit of this confidence interval was $>-10\%$, moxifloxacin was to be

considered proven not less effective than clarithromycin. A secondary efficacy analysis was performed on the bacteriological response at day 14 in microbiologically valid patients. Furthermore, all patients recorded as clinical or bacteriological success at day 14 were included in an analysis of clinical and bacteriological response at follow-up.

A secondary efficacy variable, the bacteriological response at day 14, was analysed exploratorily for the subgroup of microbiologically evaluable patients. All patients recorded as clinical or bacteriological success at day 14 were included in a secondary exploratory analysis of bacteriological and clinical response at follow-up. Ninety-five per cent confidence intervals for the differences of responses were calculated using the Mantel–Haenszel weighting scheme.

In order to assess the impact of several prospectively defined prognostic factors (age, numbers of exacerbations in previous year, coexistent cardiopulmonary disease, concomitant steroid medication, presence of airway obstruction) on the clinical cure rate at day 14, a logistic regression model was applied, considering treatment effect and all of the prognostic factors. For each of the prognostic factors an exploratory significance test was performed. To check whether substantial treatment differences were present in prognostic subgroups, the treatment differences were analysed using a logistic regression model considering a treatment effect only.

The Mantel-Haenszel chi-square test was used to calculate *P* values for the correlation between clinical and bacteriological responses. In addition, the corresponding correlation coefficients (Spearman) were calculated.

The safety analysis was performed on all patients who had received at least one dose of study drug, irrespective of follow-up examinations (equals ITT population). The incidence and severity of adverse events and abnormal laboratory values were examined and compared descriptively. All laboratory data were analysed by descriptive statistics including identification of laboratory data outside normal ranges.

Results

Disposition of patients

A total of 750 patients were enrolled into the study from November 1996 to May 1997. Three-hundred and seventy-six of these patients were randomized to moxifloxacin and 373 to clarithromycin; one patient was not randomized. Five patients were excluded from the ITT/safety analysis (three of these patients received no study medication, one patient had no information of study medication treatment documented and one patient was not randomized). Thus, 745 patients were assigned to the ITT population (374 in the moxifloxacin group and 371 in the clarithromycin group). Of these, 649 met the predetermined criteria for the efficacy-evaluable population (322 in the moxifloxacin group and 327 in the clarithromycin group). The major reasons for excluding patients from the efficacy-evaluable population were insufficient duration of therapy (moxifloxacin 24 patients, clarithromycin 14), essential data missing or invalid (moxifloxacin 17, clarithromycin 11) and violation of inclusion/exclusion criteria (moxifloxacin five, clarithromycin eight). There were 51 premature treatment discontinuations in the study, 32 in the moxifloxacin group and 19 in the clarithromycin group ($P = 0.06$, not significant). The major reasons for treatment withdrawal were adverse events (moxifloxacin 23 patients, clarithromycin 14) and non-compliance (moxifloxacin four, clarithromycin one).

Demographic and baseline characteristics

In both the efficacy-evaluable population and the ITT population, the two treatment groups were comparable with regard to demographic and baseline characteristics, and the treatment groups were homogeneous ($P > 0.05$ for all comparisons). The demographic data of the efficacy-evaluable population are summarized in Table I. Most of the patients were receiving concomitant medication, usually for a respiratory or cardiovascular disorder.

The spectrum of bacterial organisms isolated from sputum was similar in the two treatment groups for both the efficacy-evaluable and the ITT populations (data not shown). A total of 342 pre-therapy organisms classified as 'causative' for the present AECB were cultured from sputum of 287 patients (38.5% of the ITT population). Of these patients, 240 (83.6%) had one sputum pathogen, 39 (13.6%) had two pathogens and eight (2.8%) had more than two pathogens. The most common isolates were *H. influenzae* (37%), *S. pneumoniae* (31%), *M. catarrhalis* (18%), *Haemophilus parainfluenzae* (6%) and *Staphylococcus aureus* (6%). Other more rarely isolated pathogens included Enterobacteriaceae and *Pseudomonas* spp., Table II shows the pre-treatment MICs for the most frequent causative organisms. None of the pre-treatment isolates had MICs of moxifloxacin >1 mg/L (proposed resistance breakpoint for moxifloxacin, MIC $\geq$ 4 mg/L). Forty-nine isolates were resistant to clarithromycin (MIC $\geq$ 8 mg/L): 23 *Haemophilus* spp., 17 Enterobacteriaceae, four *Pseudomonas* spp., four *Streptococcus* spp. (three *S. pneumoniae* with an MIC of 256 mg/L) and one *M. catarrhalis* sp.

Clinical response

The clinical responses of the efficacy-evaluable patients at days 7, 14 and 28–35 are listed in Table III. At the day 14 primary efficacy assessment, 89.1% of patients in the moxifloxacin group and 88.4% of patients in the clarithromycin group were considered clinically cured. The 95% CI (–3.9%, 5.8%) confirmed that moxifloxacin treatment was clinically equivalent to clarithromycin treatment. Of the patients considered cured or improved at the end of treat-

Table I. Demographic data of the efficacy-evaluable study population

Characteristic	Moxifloxacin ($n = 322$)	Clarithromycin ($n = 327$)
Race (No. (%) of patients)		
caucasian	245 (76.1)	256 (78.3)
oriental	1 (0.3)	2 (0.6)
not reported	76 (23.6)	69 (21.1)
Gender (No. (%) of patients)		
male	191 (59.3)	191 (58.4)
female	131 (40.7)	136 (41.6)
Age (mean ± S.D.) (years)	60.0 ± 14.0	60.2 ± 13.5
Weight (mean ± S.D.) (kg)	73.0 ± 15.6	72.4 ± 15.8
Diagnosis of chronic bronchitis (years ago)		
0–10	210 (65.2)	212 (64.8)
>10	112 (34.8)	115 (35.2)
Smoking history		
never smoked	78 (24.2)	77 (23.5)
previous smoker	114 (35.4)	128 (39.1)
current smoker	130 (40.4)	122 (37.3)
FEV_1		
⩽75% of normal	257 (79.8)	254 (77.7)
>75% of normal	59 (18.3)	70 (21.4)
not reported	6 (1.9)	3 (0.9)
Evidence of coexistent cardiopulmonary disease		
no	297 (92.2)	299 (91.4)
yes	25 (7.8)	28 (8.6)
Number of AECBs in previous year		
<3	162 (50.3)	167 (51.1)
at least 3	160 (49.7)	160 (48.9)
Classification of presenting AECB[a]		
Type 1 AECB	218 (67.7)	225 (68.8)
Type 2 AECB	104 (32.3)	102 (31.2)

[a]According to Anthonisen *et al.*[4] Type 1: presence of all three symptoms, sputum purulence, increased sputum volume and increased dyspnoea. Type 2: any two of these three symptoms.

ment (day 7), 5.6% in the moxifloxacin group and 5.9% in the clarithromycin group clinically relapsed up to the day 14 visit. At the follow-up visit (days 28–35) of the patients clinically cured at day 14, 89.2 and 88.9% were still considered to be clinically cured in the moxifloxacin and clarithromycin groups, respectively.

The clinical cure rates at day 14 were slightly lower in the subgroup of microbiologically valid patients than in the group of all efficacy-evaluable patients. In the moxifloxacin group, 98 of 115 patients (85.2%) were considered clinically cured as compared with 97 of 114 patients (85.1%) in the clarithromycin group.

A number of additional efficacy analyses regarding the clinical response at day 14 were performed on prospectively defined prognostic subgroups of the efficacy-evaluable population. The results are shown in Table IV. Significant differences were found for some comparisons of the whole group, but not between treatments. The analyses of number of AECBs in previous year, coexistent cardiopulmonary disease and concomitant steroid medication achieved nominal P values <0.05 and thus provided some evidence for an influence of these factors on the cure rate. Furthermore, the results indicate that the clinical cure rate was improved in case of less than three AECBs in the previous year, no coexistent cardiopulmonary disease and no concomitant steroid medication. In none of the prognostic subgroups was a nominally significant difference between the treatment groups, i.e. a corresponding P value <0.05, detected. The largest difference between the treatment groups was observed for coexistent cardiopulmonary disease, which (as opposed to no coexistent cardiopulmonary disease) led to excess failure rates of 6% in the moxifloxacin group and 22% in the clarithromycin group. However, the patient numbers were very small so that the test for treatment difference did not provide a reasonable power.

Table II. Pre-treatment minimal inhibitory concentrations for the most frequent causative organisms

Species	Study drug	Number of tested organisms	MIC_{90} (mg/L)	MIC range (mg/L)
S. aureus	moxifloxacin	16	0.125	0.016–0.25
	clarithromycin	16	0.25	0.016–0.5
S. pneumoniae	moxifloxacin	86	0.25	0.016–0.5
	clarithromycin	86	2	0.016–256
H. influenzae	moxifloxacin	105	0.125	0.008–0.5
	clarithromycin	104	16	0.032–256
H. parainfluenzae	moxifloxacin	16	0.25	0.008–0.5
	clarithromycin	16	128	0.016–256
M. catarrhalis	moxifloxacin	50	0.25	0.008–1
	clarithromycin	51	0.5	0.016–16

Table III. Clinical responses in efficacy-evaluable patients

		Number (%) of patients	
	Clinical response	moxifloxacin	clarithromycin
Day 7	patient number	$n = 322$	$n = 327$
	cure	142 (44.1)	162 (49.5)
	improvement	162 (50.3)	145 (44.3)
	failure	17 (5.3)	17 (5.2)
	indeterminate	1 (0.3)	3 (0.9)
Day 14[a]	patient number	$n = 322$	$n = 327$
	cure	287 (89.1)	289 (88.4)
	failure/relapse	35 (10.9)	38 (11.6)
Day 28–35[b]	patient number[c]	$n = 287$	$n = 289$
	cure	256 (89.2)	257 (88.9)
	relapse	23 (8.0)	26 (9.0)
	indeterminate	8 (2.8)	6 (2.1)

[a]95% CI for the difference of the clinical cure rates (–3.9%, 5.8%).
[b]95% CI for the difference of the clinical cure rates (–3.9%, 5.4%).
[c]Only patients with clinical cure at day 14.

FEV_1 values in the efficacy-evaluable population improved slightly during therapy. Whereas before treatment only 18.3 and 21.4% of patients in the moxifloxacin and clarithromycin group, respectively, had an FEV_1 result of >75% of the normal value, the corresponding figures for the post-treatment FEV_1 assessments were 24.5% (moxifloxacin) and 31.2% (clarithromycin) at day 7, and 25.5% (moxifloxacin) and 30.9% (clarithromycin) at day 14.

All efficacy analyses were also performed on the ITT population. The clinical response results for the efficacy-evaluable population, and subgroups were generally confirmed for the ITT population, although clinical success rates were slightly lower than in the respective analysis for the efficacy-evaluable patients; this was mainly due to the inclusion of missing results into the 'non-success' groups of the ITT efficacy analyses which were performed as 'success' versus 'non-success'. The clinical success rates for the ITT population at day 14 were 80.8% for the moxifloxacin group and 83.0% for the clarithromycin group (95% CI, –7.7%, 3.3%).

Bacteriological results

The bacteriological results by patient at day 7, day 14 and at follow-up (days 28–35) are shown in Table V for microbiologically valid patients. The 95% CIs for the group comparisons at day 7 (8.5%, 27.7%) and day 14 (3.6%, 26.9%) indicated superiority of moxifloxacin over clarithromycin with regard to the bacteriological results by patient.

Table IV. Clinical cure rates at day 14 in efficacy-evaluable patients by prognostic subgroup

	Number of patients clinically cured/total number of patients (%)	
Subgroup	moxifloxacin ($n = 322$)	clarithromycin ($n = 327$)
Age ($P = 0.081$)[a]		
<60 years	120/138 (87.0)	128/146 (87.7)
at least 60 years	167/184 (90.8)	161/181 (89.0)
Number of AECBs in previous year ($P = 0.043$)[a]		
<3	149/162 (92.0)	153/167 (91.6)
at least 3	138/160 (86.3)	136/160 (85.0)
Coexistent cardiopulmonary disease ($P = 0.010$)[a]		
no	266/297 (89.6)	270/299 (90.3)
yes	21/25 (84.0)	19/28 (67.9)
Concomitant steroid medication[b] ($P = 0.027$)[a]		
no	147/162 (90.7)	184/199 (92.5)
yes	140/160 (87.5)	105/128 (82.0)
Presence of airways obstruction[c] ($P = 0.082$)[a]		
no	84/91 (92.3)	92/97 (94.9)
yes	185/210 (88.1)	183/213 (85.9)
not reported	18/21 (85.7)	14/17 (82.4)

[a]*P* values indicate significance level of results from test checking for an influence of the prognostic factors (presence versus absence of the factor) on the clinical cure rate at day 14.
[b]Inhaled, oral or intravenous steroids.
[c]Defined by FEV_1 at follow-up (day 28–35): obstruction, $FEV_1 \leq 75\%$ of normal value; no obstruction, $FEV_1 > 75\%$ of normal value.

Table V. Bacteriological results in microbiologically valid patients

		Number (%) of patients	
	Bacteriological response	moxifloxacin	clarithromycin
Day 7[a]	patient number	$n = 115$	$n = 114$
	success	105 (91.3)	78 (68.4)
	failure	8 (7.0)	26 (22.8)
	indeterminate	2 (1.7)	10 (8.8)
Day 14[b]	patient number	$n = 115$	$n = 114$
	success	89 (77.4)	71 (62.3)
	failure	26 (22.6)	43 (37.7)
Day 28–35[c]	patient number[d]	$n = 89$	$n = 71$
	success	71 (79.8)	55 (77.5)
	failure	17 (19.1)	10 (14.1)
	indeterminate	1 (1.1)	6 (8.5)

[a]95% CI for the difference of the bacteriological success rates (8.5%, 27.7%).
[b]95% CI for the difference of the bacteriological success rates (3.6%, 26.9%).
[c]95% CI for the difference of the bacteriological success rates (–15.7%, 8.8%).
[d]Only patients with bacteriological success at day 14.

For those patients classified as bacteriological successes at day 14, bacteriological success rates were similar at the follow-up assessment in both treatment groups (79.8% for moxifloxacin versus 77.5% for clarithromycin).

The detailed bacteriological results for the three most frequent individual pathogens at day 14 are shown in Table VI for microbiologically valid patients. Clarithromycin therapy was associated with a higher persistence rate for *H. influenzae* than moxifloxacin (32.6% versus 2.3%), whereas the numbers of persisting *S. pneumoniae* and

Table VI. Bacteriological results at day 14 for individual pathogens in microbiologically valid patients

Pre-treatment pathogen and bacteriological response category	Number of pathogens (%)	
	moxifloxacin	clarithromycin
H. influenzae		
eradication	23 (52.3)	4 (9.3)
presumed eradication	17 (38.6)	19 (44.2)
eradication with recurrence	1 (2.3)	6 (14.0)
persistence	1 (2.3)	14 (32.6)
presumed persistence	2 (4.5)	0
S. pneumoniae		
eradication	12 (31.6)	14 (38.9)
presumed eradication	20 (52.6)	21 (58.3)
eradication with recurrence	3 (7.9)	0
persistence	1 (2.6)	1 (2.8)
presumed persistence	2 (5.3)	0
M. catarrhalis		
eradication	6 (37.5)	13 (54.2)
presumed eradication	8 (50.0)	10 (41.7)
eradication with recurrence	0	0
persistence	1 (6.3)	0
presumed persistence	1 (6.3)	1 (4.2)

M. catarrhalis were very small in both groups. The numbers of strains from other bacterial species isolated in this study were too low to allow a meaningful assessment of the treatment effects.

Superinfections occurred in one of the 115 microbiologically valid patients in the moxifloxacin group (one case of *S. aureus*) and in nine of the 114 microbiologically valid patients (11 isolates) in the clarithromycin group (four cases of *H. influenzae*, two cases of *S. aureus*, one case each of *H. parainfluenzae*, *Citrobacter freundii*, *Klebsiella pneumoniae*, *Pasteurella* sp. and *P. aeruginosa*).

By day 14, nine of the 123 organisms in the moxifloxacin treatment group that were eradicated at day 7 were re-isolated (bacteriological relapse rate of 7.3%) and eight of the 106 organisms in the clarithromycin treatment group (7.5%). After day 14, six of 111 organisms in the moxifloxacin treatment group that were eradicated at day 14 were re-isolated (5.4%) and six of 106 organisms in the clarithromycin treatment group (5.7%).

In the moxifloxacin group, MICs measured pre-treatment and at day 7 (immediately post-treatment) were documented for five of the six persisting organisms. One *H. influenzae*, one *M. catarrhalis* and one *P. aeruginosa* isolate had the same MICs of moxifloxacin before and after therapy. One *Klebsiella oxytoca* and one *P. aeruginosa* showed an MIC increase of two dilution steps. In the clarithromycin group, MICs measured pre-treatment and at day 7 were documented for 19 of the 21 persisting organisms. One *Haemophilus* sp. and two *Escherichia coli* isolates had the same MICs of clarithromycin before and after therapy. Thirteen *H. influenzae* showed a median MIC increase of one dilution step during therapy. One *K. oxytoca* demonstrated an MIC increase of one dilution step, one *P. aeruginosa* showed an MIC increase of two dilution steps and one *S. pneumoniae* in the clarithromycin group had an increase in MIC of clarithromycin of seven dilution steps.

Correlation between clinical response and bacteriological results

Combining the microbiologically valid cases of both treatment groups showed that 155 of 195 patients (80%) clinically cured at day 14 were also bacteriological successes, including 92 cases in which the eradication was a presumed result in that the patient was cured and sputum was not available for culture; 29 of 34 patients (85%) with clinical failure at day 14 were also bacteriological failures, including nine cases in which the persistence was a presumed result ($P = 0.001$, correlation coefficient 0.50).

The exclusion of all patients with a bacteriological result of presumed eradication or presumed persistence from the analysis revealed that 63 of 103 patients (61%) clinically cured at day 14 were also bacteriological successes. Twenty of 25 patients (80%) with clinical failure at day 14 were also bacteriological failures ($P = 0.001$, correlation coefficient 0.33).

Relationship between bacterial resistance and treatment outcome

In the group of microbiologically valid patients randomized to therapy with clarithromycin, 57 patients had a pre-treatment sputum pathogen in-vitro susceptible to clarithromycin (MIC $\leqslant$ 2 mg/L) and 43 had at least one pathogen in-vitro resistant to clarithromycin (MIC $\geqslant$ 8 mg/L). The bacteriological success rates by patient were 42 of 57 patients (73.7%) with clarithromycin-susceptible organisms versus 21 of 43 patients (48.8%) with clarithromycin-resistant organisms ($P = 0.013$). The corresponding clinical success rates were 49 of 57 patients (86.0%) with clarithromycin-susceptible organisms versus 38 of 43 patients (88.4%) with clarithromycin-resistant organisms ($P = 0.773$).

Alternative antibacterial therapy

Alternative antibacterial therapy was documented for 40 efficacy-evaluable patients in the moxifloxacin group and for 48 patients in the clarithromycin group; it was clinically successful in 36 cases in the moxifloxacin group and in 32 cases in the clarithromycin group.

Adverse events

All patients who took at least one dose of study drug were included in the safety analysis. Adverse events were reported for 165 of 374 patients (44.1%) in the moxifloxacin group and for 172 of 371 patients (46.4%) in the clarithromycin group. Drug-related adverse events (defined as events possibly or probably related to study drug) were reported for 80 patients (21.4%) in the moxifloxacin group and for 82 patients (22.1%) in the clarithromycin group. Considering only drug-related adverse events, the most frequently affected body systems in COSTART terms were the digestive system, the body as a whole and the nervous system. Drug-related adverse events occurring at an incidence of at least 2% in either treatment group are listed in Table VII. No event of phototoxicity was reported in the study. No diarrhoea case was documented to be caused by *Clostridium difficile*.

Three deaths occurred in the study course. In the moxifloxacin treatment group, a patient who received study drug for one day developed pneumonia on the same day and died 1 day later after stopping the study medication. In the clarithromycin group, the two deaths were not considered drug-related. Serious adverse events were reported in 14 patients (3.7%) in the moxifloxacin group and in 11 patients (3.0%) in the clarithromycin group. Only two serious adverse events in the moxifloxacin group (pneumonia and urticaria with asthma) and one in the clarithromycin group (jaundice) were considered to be drug related. Premature discontinuation of study drug therapy due to an adverse event occurred in 23 patients (6.0%) in the moxifloxacin group and in 14 patients (4.0%) in the clarithromycin group (difference not statistically significant).

No unusual or unique laboratory findings were reported. An analysis of each of the standard laboratory parameters tested showed no major differences between the treatment groups with regard to relevant alterations between pretherapy and the end of therapy. No treatment-related differences were detected in the analysis of vital signs (body temperature, blood pressure, heart rate).

The numbers of hospitalizations during the study were 25 patients (6.7%) in the moxifloxacin treatment group and 23 patients (6.2%) in the clarithromycin treatment group.

Discussion

Empirical antibiotic treatment of AECB has generally been accepted as standard practice due to the recognized inaccuracies of sputum culture and the time required before culture results are available. Accumulating data suggest that there seems to be a benefit associated with it, especially for more severely ill patients.[4,5] Acknowledging this, recent guidelines state that antibiotic treatment of AECB should be initiated if bacterial infection is suspected.[1,23] Since treatment is empirical, the activity of the drug against expected bacterial pathogens is a key factor

Table VII. Drug-related adverse events reported at a frequency of at least 2% in either treatment group

	Number (%) of patients	
Adverse event	moxifloxacin ($n = 374$)	clarithromycin ($n = 371$)
nausea	20 (5.3)	15 (4.0)
diarrhoea	11 (2.9)	15 (4.0)
taste perversion	0 (0)	13 (3.5)
dizziness	12 (3.2)	4 (1.1)
headache	7 (1.9)	10 (2.7)
abdominal pain	8 (2.1)	8 (2.2)

influencing the choice of antibiotic. Other considerations include a favourable pharmacokinetic and tissue penetration profile, allowing the compound to achieve high concentrations at the site of infection, good compliance with the treatment regimen and the adverse event profile of the drug (the latter may impact on the former). Traditionally, β-lactams or macrolides have been used as antibiotics of first choice in AECB. Quinolone antibacterials have been considered as reserve drugs, particularly due to a perceived lack of efficacy of this class against *S. pneumoniae*. However, the selection of appropriate antibiotics for empirical therapy of AECB is complicated by changing resistance patterns of causative pathogens.[12,24,25]

The results of this trial indicate that a 5 day course of moxifloxacin at a dose of 400 mg od is as effective as a 7 day course of the macrolide antibiotic clarithromycin at a dose of 500 mg bd in the treatment of AECB. Both treatments gave high clinical success rates in the efficacy-evaluable population immediately after the end of treatment (94.4% for moxifloxacin and 93.8% for clarithromycin at day 7) and 7 days after the end of treatment (89.1% for moxifloxacin and 88.4% for clarithromycin at day 14). In those patients successfully treated, clinical cure was maintained up to the follow-up visit 21–28 days after the end of treatment in 89.2 and 88.9% for moxifloxacin and clarithromycin, respectively. These clinical success rates are comparable to published experience,[26–30] although it should be noted that in many other trials the patient inclusion criteria were less strict than in the present investigation.

Prognostic subgroups potentially associated with a higher risk of treatment failure[31,32] were analysed separately. The corresponding *P* values indicate that whereas the age of a patient and the degree of airway obstruction did not have any impact on the therapeutic outcome, patients with at least three AECBs in the previous year, patients with concomitant steroid use and patients with coexistent cardiopulmonary disease had a worse clinical outcome than those without these risk factors. Although differences in clinical cure rates were seen in the prognostic subgroups between the two treatments, these were not demonstrated to be statistically significant. Patients with coexistent cardiopulmonary disease had a better clinical outcome with moxifloxacin than with clarithromycin (16% more failures with clarithromycin), but the patient numbers in this subgroup were very small, which is associated with a low power for the test for treatment difference. Future clinical trials in AECB should focus on patient groups with a higher risk of treatment failure; it seems likely that an efficacy difference between two antibiotic regimens can more readily be demonstrated in such a patient population.[2,32]

The percentage of patients with causative bacterial organisms isolated pre-treatment was 35% for microbiologically valid patients. Although this compares well with rates published for other AECB trials[27–30,33] which range from 17 to 67%, the figure is disappointing, since rigorous patient selection was performed using the criteria defined by Anthonisen *et al.*[4] and sputum transportation to microbiological laboratories took place within the commonly recommended time frame of 24 h under appropriate conditions. *H. influenzae* was the most frequent pathogen, followed by *S. pneumoniae* and *M. catarrhalis*. Notably, no strains resistant to moxifloxacin were detected in this trial while 49 pre-treatment isolates were resistant to clarithromycin. In the present study, moxifloxacin was superior to clarithromycin in the overall bacteriological success rates by patient immediately after the end of therapy (day 7) and at day 14 (91 versus 68% and 77 versus 62% for moxifloxacin and clarithromycin at days 7 and 14, respectively). The rates in both groups at the day 7 and 14 assessments are in the range of the variable figures reported in the literature for other AECB studies.[26–29,34] Notably, a decline of the bacteriological success rates from immediately after the end of therapy to 1 to 2 weeks after the end of therapy was also reported for other studies[27] and may reflect in the majority of patients a recolonization of sputum with low numbers of organisms rather than a recurrence of pathogens in numbers high enough to cause clinical symptoms.

Moxifloxacin was more active than clarithromycin against Gram-negative aerobic pathogens. The low bacteriological efficacy rate of clarithromycin against *H. influenzae* raises the question of the usefulness of this agent in empirical treatment regimens for conditions where this pathogen is prevalent and should be explored further.

There was a statistically significant correlation between bacteriological success (including and excluding presumed bacteriological responses) and clinical success when all microbiologically valid patients were included in a combined analysis; this was maintained when the two antibiotics were analysed separately (data not shown). This analysis supports the contention that bacterial infection is an important stimulus of airway inflammation in AECB. One criticism of the study would be that investigators were asked to judge whether a bacterial isolate was a pathogen. This criterion was inserted to avoid commensal flora such as *Streptococcus viridans* being included, and the experience of the investigators was utilized, which reflects the 'real life' situation. Quite a large number of patients, 40 of 229 (18%), clinically recovered despite persistent infection. This result may explain why, although moxifloxacin was superior in bacteriological eradication, this was not translated into improved clinical outcome in comparison with clarithromycin. Bacterial counts would need to be performed to determine whether the bacterial load had fallen in patients with persistent infection. This was suggested by Monso *et al.*[35] who studied chronic bronchitis patients during a stable phase and during an exacerbation. They showed, using the protected specimen brush technique, that some patients were chronically colonized during a stable phase, but bacterial counts were higher during exacerbations. Another explanation would be an anti-inflammatory effect of the macrolide antibiotic treatment

which could lead to the resolution of the AECB in the presence of persistent infection.[36] This could also possibly explain the finding that patients with sputum pathogens resistant to clarithromycin had a statistically significantly higher bacteriological failure rate to clarithromycin therapy, but not a higher clinical failure rate when compared with patients with sputum pathogens susceptible to clarithromycin.

Both study drugs were generally well tolerated, and drug-related adverse events were usually mild to moderate in intensity and reported at comparable rates in both treatment groups (21 and 22% in the moxifloxacin and clarithromycin groups, respectively). Most of these events were related to the digestive or the nervous system.

Notably, no case of phototoxicity was reported in the study. The occurrence of phototoxic reactions has been described for most quinolones that are available or in development.[37] The fact that no case of sunburn or other skin reaction to light was reported confirmed the finding of a recent phase I human volunteer phototest study, in which moxifloxacin was found to have no photosensitizing potential at all.[38]

The higher rate of treatment withdrawals due to adverse events in the moxifloxacin group (6%) compared with the clarithromycin group (4%) was mainly attributed to dizziness and nausea. However, the qualitative profile of adverse events leading to discontinuation of study drug therapy was very similar between the treatment groups.

In summary, this study has shown that a 5 day course of moxifloxacin given orally at 400 mg od is clinically equivalent and bacteriologically superior to a 7 day course of clarithromycin given orally at 500 mg bd for the treatment of patients with AECB. All pre-treatment isolates were susceptible to moxifloxacin, whereas 49 were resistant to clarithromycin. The once-daily adminstration schedule and short treatment duration of moxifloxacin may have compliance advantages over existing therapies in a less controlled setting, such as community clinical practice.

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