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Moxifloxacin versus levofloxacin against acute exacerbations of chronic bronchitis: The Latin American Cohort

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Summary We compared the efficacy and safety of moxifloxacin and levofloxacin for the treatment of patients with acute exacerbations of chronic bronchitis (AECB) using a prospective, randomized, double blind, parallel-group clinical trial design. A total of 563 patients with AECB were enrolled (437 efficacy-valid) at 34 centers in Mexico, Argentina, Brazil, Colombia, and Peru. Patients were randomized to oral therapy with either moxifloxacin 400 mg once daily for 5 days or levofloxacin 500 mg once daily for 7 days. Clinical success was achieved in 201 out of 221 (91.0%) patients in the moxifloxacin group, and in 203 out of 216 (94.0%) in the levofloxacin group,

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indicating that moxifloxacin is equivalently effective to levofloxacin. Bacteriologic eradication or presumed eradication was also similar in the two treatment groups: 92.8% in the moxifloxacin group and 93.8% in the levofloxacin group. Nausea was the most common drug-related adverse event in each treatment group. The rate of discontinuation because of adverse events was very low ($\leqslant$2%). In conclusion, a 5-day course of moxifloxacin is clinically and bacteriologically equivalent to a 7-day course of levofloxacin in the treatment of patients with AECB. The short treatment duration with moxifloxacin may have compliance advantages over other currently used therapies in the 'real-life' clinical setting.

Introduction

Acute exacerbations of chronic bronchitis (AECB) present as a worsening of respiratory symptoms, and can be precipitated by a variety of factors including air pollutants, allergens, viruses and, in 50–60% of cases, by bacterial infection.[1,2] Chronic bronchitis and accompanying exacerbations are associated with a high socio-economic burden. The direct annual cost in the USA of treating AECB has been calculated at $1.6 billion per year, of which $1.5 billion is spent on hospitalizations.[3] Thus, new therapies that enable AECB patients to be treated primarily on an outpatient basis are likely to be associated with substantial cost savings.

A recent meta-analysis of large, placebo-controlled trials suggests a benefit of antimicrobial therapy in AECB, particularly in patients categorized as having type I symptoms (i.e., increased dyspnea, sputum volume, and sputum purulence).[4] Ideally, choice of antimicrobial therapy should be based on confirmed identification and susceptibility of the causative pathogen. However, microbiology test results are rarely available to guide initial therapy, which is consequently often empiric. This approach requires agents with activity against the bacterial pathogens most likely to be encountered, namely *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis*.[1,2,5] Antimicrobial resistance has developed rapidly over the last 20 years in each of these species, and local resistance patterns should also be taken into account when selecting appropriate therapy.

Fluoroquinolones have been considered as important options in facing growing bacterial resistance. Levofloxacin, the *S*-(−) isomer from the racemic mixture known as ofloxacin[6]; and moxifloxacin, a newer 8-methoxyquinolone, have shown enhanced in vitro activity against bacterial pathogens commonly implicated in respiratory tract infections, as well as atypical pathogens (e.g., *Mycoplasma pneumoniae)*.[6,7] The aim of the present study was to compare the clinical efficacy and safety of oral moxifloxacin 400 mg once daily for 5 days with oral levofloxacin 500 mg once daily for 7 days in the treatment of patients with AECB.

Methods

Study design

This was a prospective, multinational, double-blind, randomized, controlled, parallel-group clinical study designed to compare 5-day oral moxifloxacin therapy with 7-day oral levofloxacin therapy in the treatment of AECB. Thirty-four centers in five Latin American countries (Argentina, Brazil, Colombia, Mexico, and Peru) participated.

Patient selection

Adult patients ($\geqslant$18 years of age) were eligible for inclusion in the study if they had a diagnosis of chronic bronchitis (history of cough and sputum on most days during at least 3 consecutive months and for more than 2 successive years), with exacerbation within the previous 14 days characterized by increased cough, increased sputum production with changes in color and consistency, and mild-to-moderate dyspnea. Patients were not included if they had received recent antibiotic therapy, had other lower respiratory tract illnesses (e.g., pneumonia, bronchiectasis, tuberculosis, cystic fibrosis, or pulmonary malignancy) detected clinically and by X-ray, were pregnant or lactating, had severe hepatic, cardiac, or renal impairment, or concomitant serious illness, had a history of allergy to fluoroquinolones, or had recently participated in another clinical trial.

Antibacterial therapy

Patients were randomized in groups of four to either moxifloxacin 400 mg once daily for 5 days or levofloxacin 500 mg once daily for 7 days. Both

drugs were supplied by Bayer AG (Leverkusen, Germany). Blinding was ensured by placing either moxifloxacin 400 mg tablets or placebo tablets inside a capsule of identical appearance to that of levofloxacin 250 mg. Since levofloxacin dose consisted of two 250 mg capsules, the patients in the moxifloxacin group received for each dose one placebo capsule and one active moxifloxacin capsule during the first 5 days, and two placebo capsules for the remaining 2 days to maintain blinding.

Clinical assessments

All patients attended four visits on an outpatient basis. Evaluations were performed at entry (baseline), 3–5 days after starting therapy (on-therapy evaluation), 1–3 days after completion of therapy (end-of-therapy), and 7–14 days after completion of therapy (test of cure; primary efficacy variable). On-therapy visit could be conducted by telephone if the patient was doing well. At each visit, clinical signs and symptoms were assessed and compared to baseline, compliance with medication was checked by a medication count, and concomitant medication were recorded. Clinical response was classified as (i) resolution (total resolution of signs and symptoms related to the acute exacerbation to such an extent that no additional or alternative therapy was necessary), (ii) failure (persistence or worsening of all or most of the signs and symptoms related to the acute exacerbation, or the need for hospitalization or other antibacterial), or (iii) indeterminate (no evaluation possible). If clinical failure was documented, a sputum sample was obtained and alternate medication prescribed.

Bacteriologic assessments

Sputum samples were obtained at baseline, at test-of-cure visit (if material was available), and in cases of clinical failure. Cultures were then performed locally and isolates forwarded to a central laboratory. To be considered evaluable, sputum samples were scored according to the Murray–Washington Group 5 Score System. The susceptibility of bacterial isolates toward moxifloxacin and levofloxacin, as well as ampicillin, clarithromycin and cefuroxime, was tested using *E*-test, following manufacturers' guidelines.

Patients who provided a bacteriologically positive baseline sputum sample were included in the evaluation of bacteriologic response. Because many patients were unable to provide sputum samples at resolution, bacteriologic response was judged presumptively. Bacteriologic response was classified as (i) presumed eradication (clinical cure in the absence of a repeat sputum culture), (ii) documented eradication (absence of original pathogen in culture of sputum sample taken 1–2 weeks post-therapy), (iii) presumed persistence (clinical failure in the absence of a repeat sputum culture), (iv) persistence (presence of original pathogen in culture of sputum sample taken 1–2 weeks post-therapy), (v) superinfection (isolation of a different pathogen during therapy in a symptomatic patient), or (iv) indeterminate (no evaluation possible).

Safety assessments

At each assessment after signing the informed consent, clinical and laboratory adverse events were recorded. Severity (mild, moderate, severe), threatening to life or not, relationship to study drug (possible, probably, remote, none), and outcome were monitored until resolution. Clinical laboratory parameters (hematology, urinalysis, and chemistry) were performed on blood and urine samples obtained pre-therapy and at the post-therapy visits.

Statistical analyses

The primary efficacy variable was the clinical outcome at the test-of-cure visit in the valid per-protocol population. The primary aim of the study was to reject the null hypothesis, that a 5-day therapy with moxifloxacin 400 mg OD for 5 days was more than 10% less effective than a 7-day therapy with levofloxacin 500 mg OD. For the difference in clinical success rates, a 95% confidence interval (95% CI, moxifloxacin minus levofloxacin) was calculated using Mantel–Haenszel weights. For moxifloxacin to be considered not less effective than levofloxacin, the lower limit of this confidence interval had to be greater than −10%. The same approach was used for the bacteriological response at test-of-cure visit in the efficacy-valid or per-protocol population and for the clinical and bacteriological outcomes in the intention-to-treat population. The two treatment groups were assessed for comparability in their demographic and other baseline characteristics by standard statistical methods. Safety analysis included tabulations of type and frequency of all adverse events. All laboratory data were analyzed using descriptive statistics including identification of cases outside of normal ranges.

Results

Patient sorting

Five hundred and sixty-three patients were enrolled in the study: 279 received moxifloxacin and 284 received levofloxacin. One patient in each group was excluded from the intention-to-treat/safety analysis for not receiving study medication. Four hundred and thirty seven patients met the pre-defined criteria for the population (221 in the moxifloxacin group and 216 in the levofloxacin group). The most common reasons for exclusion from the per-protocol analysis were violation of entry criteria (moxifloxacin 25; levofloxacin 40) and missing essential data (moxifloxacin 38; levofloxacin 32). There were 45 premature discontinuations from the study (moxifloxacin 23; levofloxacin 22). The most common reasons were adverse events (moxifloxacin 5; levofloxacin 6) and lost to follow up (moxifloxacin 6; levofloxacin 7).

Demographics and baseline characteristics

Demographic data and baseline medical characteristics for the efficacy-valid population are presented in Table 1. In both the per-protocol and intention-to-treat populations, the two treatment groups were comparable with respect to baseline

Table 1 Demographics and baseline medical characteristics: efficacy-valid population.

	Moxifloxacin ($n = 221$)	Levofloxacin ($n = 216$)
Demographics		
Age, years, mean ± SD	59 ± 15	61 ± 15
Sex, no. male/female	110/111	110/106
Race, *n* (%)		
Mestizo*	143 (64.7)	149 (69.0)
Caucasian	72 (32.6)	63 (29.2)
Other/not reported	6 (2.7)	4 (1.8)
Pathological findings on chest X-ray, *n* (%)	46 (20.8)	29 (13.4)
Onset of current AECB episode, *n* (%)		
0 < 4 days prior to therapy	27 (12.2)	34 (15.7)
4 < 7 days prior to therapy	56 (25.3)	56 (25.9)
⩾7 days prior to therapy	138 (62.4)	126 (58.3)
History of smoking, n (%)		
Never smoked	68 (30.8)	62 (28.7)
Past smoker	104 (47.1)	111 (51.4)
Current smoker	49 (22.2)	62 (19.9)
Average no. of cigarettes/day†, mean ± SD	17.92 ± 14.40	14.77 ± 12.02
Duration of smoking‡, years, mean ± SD	32.73 ± 16.59	35.22 ± 15.91
Clinical signs and symptoms		
Increased purulent/mucopurulent sputum, *n* (%)	221 (100)	216 (100)
Cough, *n* (%)		
Mild	23 (10.4)	24 (11.1)
Moderate	149 (67.4)	152 (70.4)
Severe	49 (22.2)	40 (18.5)
Dyspnea, *n* (%)		
Mild	78 (35.3)	88 (40.7)
Moderate	143 (64.7)	128 (59.3)
Fever, *n* (%)	37 (16.7)	37 (17.1)

*Mixed race (Caucasian and indigenous population).
†For smokers.
‡Past and current smokers only.

demographics and medical history/symptomatology. In total, 184 patients in the moxifloxacin group and 180 patients in the levofloxacin group had concomitant medication that began before the study treatment was initiated. Fifty-four patients (19.4%) in the moxifloxacin group and 68 (24.0%) in the levofloxacin group had concomitant medication (excluding antibacterial agents) started during the study. The majority of the concomitant medications were drugs such as β_2-selective adreno-receptor agonists used for respiratory tract indications.

Clinical response

For the per-protocol population, clinical improvement was reported for 96.8% of moxifloxacin recipients and 96.3% of levofloxacin recipients at the end-of-therapy visit (Table 2). At the test-of-cure visit clinical resolution (success) was achieved in 91.0% and 94.0% of patients in the moxifloxacin and levofloxacin groups, respectively (95% CI −7.30%, 2.29%) indicating that moxifloxacin was not less effective than levofloxacin. This conclusion was confirmed in the intention-to-treat population: 80.9% clinical success in the moxifloxacin group versus 83.7% in the levofloxacin group at test-of-cure visit (95% CI −8.95, 3.43). Likewise clinical success was unrelated to concomitant use of corticosteroid or coexistence of cardiopulmonary disease (data not shown).

Both treatment groups experienced a substantial improvement in the signs and symptoms of AECB within the inclusion and the test-of-cure visits. The presence of increased purulent/mucopurulent sputum decreased from 100% in both groups at baseline to 28 (12.7%) of moxifloxacin patients and 15 (6.9%) of levofloxacin patients. The proportion of patients reporting moderate-to-severe cough decreased from 89.6% in the moxifloxacin group and 88.9% and levofloxacin group at baseline to 6.4% and 4.2%, respectively. The percentage of patients experiencing moderate dyspnea also decreased from 64.7% to 8.1% in the moxifloxacin group and from 59.3% to 7.4% in the levofloxacin group.

Bacteriologic results

Bacteria considered causative of AECB were cultured from the sputum of 172 moxifloxacin patients and 169 levofloxacin patients in the intention-to-treat population. Of these, 267 patients (moxifloxacin 138; levofloxacin 129) were also valid for efficacy and said to be microbiologically valid. In total, 230 microbiologically valid patients had one pathogen isolated, 36 had two, and one patient had more than two pathogens. The spectrum of organisms isolated was comparable between the two treatment groups, and most commonly included *H. influenzae*, *Klebsiella pneumoniae*, *S. pneumoniae* and *M. catarrhalis*. Antimicrobial susceptibility of isolates of these species is shown in Table 3.

Bacteriologic response at the test-of-cure visit is summarized in Table 4. Bacteriologic success was achieved in 92.8% of patients in the moxifloxacin group and 93.8% of patients in the levofloxacin group (95% CI −6.8%, 5.1%), confirming that moxifloxacin was not less effective than levofloxacin in this regard. Nine patients in the moxifloxacin group had persistent or presumed persistent bacteria at this visit, including three *H. influenzae*, two *S. pneumoniae*, one *Haemophilus parainfluenzae*, two *Staphylococcus aureus*, one *Pseudomonas*

Table 2 Clinical response rates in the efficacy-valid and intent-to-treat populations.

	Efficacy-valid population		Intent-to-treat (safety) population	
	Moxifloxacin ($n = 221$) (%)	Levofloxacin ($n = 216$) (%)	Moxifloxacin ($n = 278$) (%)	Levofloxacin ($n = 283$) (%)
End of therapy (1–3 days post therapy)				
Improvement	214 (96.8)	208 (96.3)	258 (92.8)	257 (90.8)
Failure	5 (2.3)	7 (3.2)	5 (1.8)	9 (3.2)
Indeterminate	2 (0.9)	1 (0.5)	4 (1.4)	7 (2.5)
			11 (4.0)	10 (3.5)
Test of cure (7–14 days post therapy)				
Resolution	201 (91.0)	203 (94.0)	225 (80.9)	237 (83.7)
Failure	20 (9.0)	13 (6.0)	21 (7.6)	23 (8.1)
Indeterminate	0	0	11 (4.0)	7 (2.5)
			21 (7.6)	16 (5.7)

Table 3 Antimicrobial susceptibility of typical isolated pathogens, at baseline.

	n	MOX		LEV		AMP		CLA		CEF	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
H. in	77	0.023	0.19	0.016	0.064	0.25	6	4	12	0.5	1
K. pn	40	0.056	0.19	0.047	0.25	48	>256	24	64	2.5	12
M. ca	36	0.047	0.38	0.032	0.094	0.5	2	0.064	4	0.5	3
S. pn	29	0.094	0.25	0.38	0.75	0.016	0.5	0.032	0.5	0.016	0.38

MOX, moxifloxacin; LEV, levofloxacin; AMP, ampicillin; CLA, clarithromycin; CEF, cefuroxime. *H. in, Haemophilus influenzae; K. pn, Klebsiella pneumoniae; M.* ca, *Moraxella catarrhalis; S. pn, Streptococcus pneumoniae*. MIC_{50} and MIC_{90} values in μg/mL.

Table 4 Bacteriologic response 7–14 days post therapy in the microbiologically valid population.

	No. (%) of patients	
	Moxifloxacin ($n = 138$)	Levofloxacin ($n = 129$)
Bacteriologic success	128 (92.8)	121 (93.8)
Eradication	12 (8.7)	14 (10.9)
Presumed eradication	116 (84.1)	107 (82.9)
Bacteriologic failure	10 (7.2)	8 (6.2)
Eradication+superinfection	1 (0.7)	0
Persistence	4 (2.9)	4 (3.1)
Presumed persistence	5 (3.6)	4 (3.1)

Table 5 Most common adverse events considered possibly or probably related to study drug.

Adverse event	No. (%) of patients	
	Moxifloxacin ($n = 278$)	Levofloxacin ($n = 283$)
Digestive tract	33 (11.9)	40 (14.1)
Nausea	12 (4.3)	16 (5.7)
Diarrhea	8 (2.9)	8 (2.8)
Body as a whole	19 (6.8)	7 (2.5)
Headache	7 (2.5)	4 (1.4)
Nervous system	10 (3.6)	10 (3.5)
Dizziness	2 (0.7)	2 (0.7)
Somnolence	3 (1.1)	2 (0.7)
Insomnia	1 (0.4)	4 (1.4)
Total	66 (23.7)	76 (26.9)

aeruginosa, one *Burkholderia cepacia*, and one *K. pneumoniae* (some patients had more than one pathogen). Levofloxacin failed to eradicate nine bacteria from eight patients — including two *H. influenzae*, one *H. parainfluenzae*, two *P. aeruginosa*, one *K. pneumoniae* and one *P. mirabilis*.

There was a high correlation between bacteriologic and clinical success. Of 126 moxifloxacin-treated patients classified as clinical successes, 124 (98.4%) were bacteriologic successes; of 122 levofloxacin-treated patients classified as clinical successes, 119 (97.5%) were bacteriologic successes.

Safety

The safety population included 561 patients (moxifloxacin 278; levofloxacin 283). The median

duration of exposure to therapy was 7 days in both treatment groups, with a range of 1–8 days in the moxifloxacin group and 1–7 days in the levofloxacin group. Adverse events considered possibly or probably related to study medication were reported by 66 (23.7%) patients in the moxifloxacin group and 76 (26.9%) patients in the levofloxacin group. The majority of drug-related adverse events were mild in intensity, and most commonly involved the digestive tract (Table 5). Five patients in the moxifloxacin group and six patients in the levofloxacin group prematurely discontinued treatment because of adverse events, and eight moxifloxacin-treated patients and six levofloxacin-treated patients required hospitalization for adverse events. There were four deaths during the study, none classified as related to study drug. One serious adverse event (dyspnea) was considered possibly related to treatment with moxifloxacin; one serious adverse (upper digestive tract bleeding) was classified as probably related to treatment with levofloxacin. There were no significant changes in vital signs throughout the study, and no significant between-group differences with respect to clinical laboratory parameters.

Discussion

AECB is a common and debilitating condition that can be caused by a wide range of bacterial pathogens. As the conventional microbiological assessment of etiology and antimicrobial susceptibility are time-consuming and not always reliable, antimicrobial therapy for this condition is generally instituted empirically. However, in recent years, empiric antimicrobial therapy of AECB has been complicated by the spread of antimicrobial resistance.[8,9] Indeed, although β-lactams have traditionally been the mainstay of therapy for AECB, resistance has spread rapidly through *S. pneumoniae*, and a high proportion of *H. influenzae* and of *M. catarrhalis* strains now produce β-lactamases, rendering penicillins inactive.[8] In view of this, the newer macrolides, e.g., clarithromycin and azithromycin, have become more widely used for management of AECB. However, macrolide resistance is now also well established among *S. pneumoniae*, and the activity of these agents against *H. influenzae*, one of the most important AECB pathogens, is marginal.[8]

In this study we compared the efficacy and safety of a 5-day course of the fluoroquinolone moxifloxacin with that of a 7-day course of levofloxacin. A high rate of clinical success was observed in both treatment groups. Within 1–3 days of finishing therapy, clinical success was achieved in 91% of patients treated with short-course (5-day) moxifloxacin and 94% of patients treated with levofloxacin for 7 days in the per-protocol population. Similarly at the test of cure visit, 7–14 days after finishing therapy, the short-course regimen of moxifloxacin proved to be as effective clinically as the 7-day levofloxacin regimen, with continued clinical resolution reported in over 90% of per-protocol patients in both groups. These rates are similar to those reported previously by Hautamaki and colleagues[10] in a US study of similar design (93% and 94% clinical success for moxifloxacin and levofloxacin, respectively, at test of cure). Other comparative trials have also shown a 5-day course of moxifloxacin to be as effective clinically as standard regimens of azithromycin and clarithromycin, and possibly superior to co-amoxiclav 7 days[11–13]. The shorter duration of the moxifloxacin course is also likely to have benefits in terms of improved compliance (i.e., increased likelihood that the patient will complete the entire recommended treatment course), which in theory may also reduce the opportunity for development of resistant organisms. Shorter-course therapy may also offer tolerability benefits.

In vitro and in vivo studies have shown that moxifloxacin has a broad spectrum of activity covering a wide range of bacterial pathogens implicated in community-acquired respiratory tract infections.[6,14] In the present study, moxifloxacin demonstrated potent in vitro activity against the range of causative pathogens isolated at the pre-therapy visit. Against *Streptococcus* species, such as *S. pneumoniae*, the MICs for moxifloxacin were approximately 2–3 dilutions lower than those for levofloxacin, indicating that moxifloxacin was the more potent of the two agents. Against Gram-negative pathogens, the two agents showed comparable in vitro activity. Including the present study, five double-blind and five open-label studies evaluating the efficacy of moxifloxacin in >14,000 patients with AECB have been reported so far.[10–13,15–18] Analysis of these studies gives mean overall clinical and bacteriologic success rates for moxifloxacin in AECB of 95% and 92%, respectively.

Moxifloxacin and levofloxacin had very similar adverse event profiles in the present study, with nausea being the most common drug-related event in both groups. Therapy was generally well tolerated, and the rate of premature discontinuation of study drug because of adverse events was very low in both groups (approximately 2%).

In conclusion, this study has shown that a 5-day course of moxifloxacin 400 mg once daily is

clinically and bacteriologically equivalent to a 7-day course of levofloxacin 400 mg once daily in the treatment of patients with AECB. The shorter treatment duration with moxifloxacin may have compliance advantages over other currently used therapies in the 'real-life' clinical setting.

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