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The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia

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An international multi-centre, randomized, prospective, double-blind study compared oral moxifloxacin (200 mg or 400 mg once daily for 10 days) with oral clarithromycin (500 mg, twice daily for 10 days) in the treatment of community-acquired pneumonia (CAP).

The clinical success rate in the evaluable population at the primary efficacy assessment, 3–5 days after the end of study treatment, was 93·9% in patients treated with 200 mg moxifloxacin; 94·4%, with 400 mg moxifloxacin; and 94·3%, with clarithromycin. Clinical success rates were maintained at follow-up, 21–28 days after the end of treatment: 90·7% (200 mg moxifloxacin), 92·8% (400 mg moxifloxacin) and 92·2% (clarithromycin). The 95% confidence intervals indicated that all three treatment regimens were equally effective in treating CAP. At follow-up, the 400 mg moxifloxacin dose had a slightly higher observed cure rate than the 200 mg moxifloxacin dose, but this was not statistically significant.

The most frequently isolated pathogens were *Streptococcus pneumoniae* (42%), *Haemophilus influenzae* (19%), *Haemophilus parainfluenzae* (10%), *Moraxella catarrhalis* (6%), *Klebsiella pneumoniae* (5%) and *Staphylococcus aureus* (4%). The bacteriological success rate (eradication and presumed eradication) was 72·5% (29/40) for 200 mg moxifloxacin, 78·7% (37/47) for 400 mg moxifloxacin and 70·7% (29/41) for clarithromycin.

The adverse event profile was comparable between the three treatment groups. Most adverse events, possibly or probably related to the study drug, were generally mild or moderate in severity and mostly related to the digestive system: diarrhoea, nausea and abdominal pain in 200 mg moxifloxacin patients; diarrhoea, liver function abnormalities and nausea in 400 mg moxifloxacin patients and liver function abnormalities, diarrhoea, nausea and taste perversion in clarithromycin patients. Study drugs were discontinued because of adverse events in 7/229 (3%) patients treated with 200 mg moxifloxacin, 11/224 (5%) with moxifloxacin 400 mg and 11/222 (5%) with clarithromycin.

In all assessments, moxifloxacin was at least as effective clinically, and as well tolerated as clarithromycin in the treatment of CAP. Bacteriological success rates in moxifloxacin-treated patients were greater than those of clarithromycin. Moxifloxacin, given once daily, is free of many drug–drug interactions and requires no dosage adjustments in most renal/hepatic deficient patients.

Key words: moxifloxacin; fluroquinolones; community-acquired pneumonia; treatment.

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Introduction

Pneumonia is defined as a syndrome with signs and symptoms of an acute lower respiratory illness with significant consolidation on chest radiography, which is neither pre-existing, nor of other known non-infectious cause (1). The incidence of community acquired pneumonia (CAP) has been estimated as between 1 and 5 per 1000 of the population per year, with a hospitalization rate of 22% and mortality rate of 3%. The mortality rate may increase to 16–40% in the elderly and in those with comorbidities (2,3). Thus, early diagnosis and effective antimicrobial therapy are essential in the treatment of CAP. Diagnosis is based on clinical signs and symptoms (fever, pleuritic chest pain and cough, production of mucopurulent sputum,

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tachycardia and tachypnoea), combined with chest radiography and management refined with microbiological culture (4).

The most common cause of CAP is *Streptococcus pneumoniae*, accounting for around two thirds of cases of bacteremic pneumonia (5). A wide range of other pathogens may also be implicated including *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, Gram-negative enterobacteria, *Coxiella burnetii* and *Moraxella catarrhalis*.

Initial antimicrobial therapy of CAP in outpatients is generally empirical and is based on multiple variables including severity of illness, patient age, clinical features, comorbidities, concomitant medication, exposure and the epidemiological setting. Inadequate antimicrobial therapy is a factor of poor prognosis (6). Guidelines for the management of CAP vary in different countries; the British Thoracic Society has suggested that empirical therapy should always cover *S. pneumoniae* with a preferred regimen of penicillin or amoxicillin, with erythromycin for atypical infections (7). Paradoxically, the Alexander Project 1998 confirmed that increasing resistance to penicillin and macrolides amongst strains of *S. pneumoniae* in many countries worldwide is compromising the clinical efficacy of these compounds (8). Guidelines, reflecting these changes, from the Infectious Disease Society of America (ISDA) suggest that the preferred empirical antimicrobials for most patients are macrolides (azithromycin, clarithromycin or erythromycin), fluoroquinolones (with enhanced activity against *S. pneumoniae*) or doxycycline. Alternative options, which are not active against atypical pathogens, include amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime or cefprozil) (9).

Many current antimicrobial agents need to be given more than once a day, which can lead to problems with compliance (10). Also, changing susceptibility patterns and increasing penicillin, macrolide and tetracycline resistance of *S. pneumoniae* warrant the development and evaluation of new agents.

Moxifloxacin is a new, broad spectrum 8-methoxyfluoroquinolone. It has excellent *in vitro* activity against Gram-positive pathogens, with enhanced activity against *S. pneumoniae* (compared to that of the older fluoroquinolones) and Gram-negative pathogens, including *Klebsiella pneumoniae* (11). It is highly active against other pathogens commonly involved in CAP, including *H. influenzae* and the atypical pathogens, *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae* (12–14).

Pharmacokinetic studies in animals and humans have shown that a single 400 mg oral dose of moxifloxacin achieves extensive penetration into lung tissue with the concentration in alveolar macrophages, bronchial mucosa and epithelial lining, over a 24 h period, exceeding the minimium inhibitory concentration (MIC_{90}) of most of the pathogens (including *S. pneumoniae*) involved in CAP (15).

The aim of this study was to compare the efficacy and safety of oral moxifloxacin (200 mg or 400 mg once daily for 10 days) with the standard therapy of clarithromycin (500 mg twice daily for 10 days) in the treatment of CAP.

Methods

This was a prospective, randomized, double-blind trial carried out at 50 centres in 15 countries: Austria (2), Australia (4), Germany (4), Great Britain (12), Greece (4), Hong Kong (2), Israel (3), Indonesia (2), New Zealand (1), Norway (2), Philippines (3), South Africa (5), Sweden (3), Switzerland (1) and Taiwan (2). The study was conducted from 26 November 1996 to 5 February 1998. The study protocol was prepared in accordance with the European Guidelines for Good Clinical Practice (16), national and regional regulations, and was reviewed by all appropriate national and regional ethics committees. Written informed consent was obtained from all patients prior to inclusion in the study.

PATIENTS

Patients eligible for inclusion into the study were outpatients of either sex, aged 18 years or older, with CAP. Female patients of child-bearing age had to be using a reliable contraceptive method. CAP was diagnosed clinically on the basis of chest radiographs and the presence of fever (core temperature $>38{\cdot}5^{\circ}C$ or oral temperature $>38^{\circ}C$) and/or leukocytosis ($>10\,000\,mm^3$), together with one or more of the following symptoms: productive cough, purulent sputum, dyspnoea or tachypnoea (20 breaths min^{-1}), rigors/chills, pleuritic chest pain or rales/rhonchi indicating consolidation. Patients were excluded from entry to the study if they presented with a history of hypersensitivity to either study drug or related compounds; suspected aspiration pneumonia due to vomiting; neutropenia; liver disease or renal insufficiency; AIDS; any severe infection or severe cardiac failure; severe life-threatening disease or a history of tendinopathy with fluoroquinolones. Patients were excluded if they required concomitant systemic antibacterial treatment or had received any systemic antibacterial therapy for more than 24 h immediately prior to enrolment. However, patients receiving antibiotic therapy, other than a quinolone or macrolide, for at least 72 h and who had clearly failed on that therapy could be enrolled. Female patients were excluded if they were pregnant or breast-feeding. Patients with congenital or sporadic syndromes of QTc prolongation or receiving concomitant medication known to increase the QTc interval were also excluded.

ANTIBIOTIC THERAPY

Patients fulfilling the enrolment criteria were randomized to receive either moxifloxacin 200 mg or 400 mg once daily, or clarithromycin 500 mg twice daily for 10 days. Clarithromycin was administered as two active capsules (250 mg each) in the morning and in the evening. Blinding was maintained by administration of moxifloxacin as one active

capsule (200 mg or 400 mg) and one placebo capsule in the morning, and two placebo capsules in the evening. All medications were taken orally with meals and 100 ml water.

CLINICAL AND BACTERIOLOGICAL EVALUATIONS

Patients were assessed pretherapy (day 0), during treatment (day 3–5), 3–5 days after the end of treatment (day 13–15) and at follow-up (21–28 days after the end of treatment).

Before inclusion into the study, patients were clinically examined, a full medical history obtained and a chest radiograph performed. Samples of blood and urine were collected for haematology and biochemical analysis. Blood and sputum samples were obtained to detect the presence of bacteria. Sputum or bronchial material was obtained by the following methods: sputum sample by deep expectoration; bronchial material by nasal or oral tracheal aspiration, bronchoalveolar lavage (BAL), bronchoscopic protected catheter brush (BRCB), open lung biopsy or transtracheal aspiration (TTA); or pleural fluid by pleural aspiration or tap. Only sputum samples containing ≤ 10 squamous cells and ≥ 25 leucocytes per low power field were cultured to increase the likelihood that cultured organisms were causative of CAP. All cultured organisms were identified by genus and species and all causative organisms were subjected to susceptibility testing to moxifloxacin and clarithromycin by the E-test (AB Biodisk, Sweden). Blood samples for serological testing were collected and sent to a centralized laboratory for analysis.

Clinical and bacteriological assessments were repeated during and at the end of treatment and at follow-up. An additional X-ray at the end of treatment was optional.

The primary efficacy evaluation was clinical response, 3–5 days after the end of study treatment and was assessed as cure (resolution of clinical signs and symptoms related to infection and not requiring further antibiotic therapy) or failure (failure to respond, or insufficient response to study antibiotics requiring modification in antibiotic therapy, or resulting in death from the primary diagnosis) based on scoring the clinical signs and symptoms.

A secondary assessment of clinical response at follow-up, 21–28 days after study treatment, was assessed as cure (resolution of clinical signs and symptoms maintained throughout follow up and not requiring further antibiotic therapy), failure or indeterminate. Clinical failures at the end of therapy were carried forward to the follow-up assessment and also included recurrence/relapse (initial or partial resolution of clinical signs and symptoms within the study drug treatment period but with recurrence of clinical condition requiring further antibiotic therapy within 21–28 days after study drug treatment).

Bacteriological response, 3–5 days after the end of study drug treatment, was a secondary evaluation and was assessed as eradication (causative organism not present at the end of therapy and patient had improved clinically), presumed eradication (no sample for bacteriological assessment obtained in patients who had improved), persistence (causative organism still present at the end of therapy), superinfection (presence of a different pathogen during therapy or immediately after therapy together with signs and symptoms of infection requiring treatment with another antibacterial agent), missing assessment or indeterminate. Bacteriological assessment at follow-up, 21–28 days after study drug treatment was assessed as continued eradication, reinfection (eradication of the original organism by end of therapy but with re-isolation of a new pathogen within or at the 21–28 day follow-up and associated with clinical relapse), recurrence (eradication of the original organism by end of therapy but with re-isolation of the same causative pathogen within or at the 21–28 day follow-up and associated with clinical relapse), persistence, presumed persistence, missing assessment or indeterminate.

SAFETY EVALUATIONS

Safety analysis was performed on all patients who had received at least one dose of study drug. Adverse events were coded using COSTART terms and were assessed for frequency, duration, severity, outcome and relationship to study drug.

STATISTICAL ANALYSIS

The three treatment groups were compared for the primary efficacy variable by calculating the weighted Mantel–Haenszel point estimates and 95% confidence intervals for the difference in clinical cure rates. A difference of more than 15% in the lower limit was required to prove that moxifloxacin was no less effective than the comparator, clarithromycin.

Results

A total of 678 patients were recruited into this study from 50 centres in 15 countries. The 50 centres were grouped into five geographical regions: HongKong/Taiwan/Indonesia/Philippines (nine centres, 77 patients); Greece/Israel (seven centres, 156 patients); Germany/Austria/Switzerland/Norway/Sweden (12 centres, 94 patients); Great Britain/Australia/New Zealand (17 centres, 150 patients) and South Africa (five centres, 201 patients). A total of 675 patients were randomized to receive treatment and were included in the safety and intention to treat (ITT) analyses: 229 (34%) patients received moxifloxacin 200 mg, 224 (33%) received moxifloxacin 400 mg and 222 (33%) received clarithromycin. Three patients withdrew from the study: one patient in the moxifloxacin 200 mg group was not treated with the study drug and two patients in the clarithromycin group had no post baseline assessments.

Five hundred and thirty-one patients (77%) were evaluable for efficacy and safety and were included in the per protocol (PP) analyses: 180 of 229 patients (79%) in the 200 mg moxifloxacin group, 177 of 224 (79%) in the 400 mg moxifloxacin group and 174 of 222 (78%) in the clarithromycin group. The main reasons for exclusion from

the efficacy analysis did not differ significantly between the groups and included essential data missing (106 patients), non-compliance with study drug (33) and violation of the inclusion or exclusion criteria (24).

In the PP and ITT populations, the three treatment groups were comparable with respect to demographic parameters (age, sex, weight and body mass index) concomitant medication and comorbid conditions. Furthermore, there were no significant differences between the treatment groups with regards to baseline signs and symptoms of CAP (Table 1).

Approximately 30% of patients were hospitalized, 25% had pre-existing respiratory disease and 58% were either current or previous smokers. All evaluable patients had pathological findings consistent with pneumonia on pre-therapy radiograph including unilateral infiltrate (85%), bilateral infiltrate (13%) and pleural effusion (1%).

CLINICAL RESPONSE

The clinical success rate, defined as cure, in the evaluable population at the end of treatment was 93·9% (200 mg moxifloxacin), 94·4% (400 mg moxifloxacin) and 94·3% (clarithromycin). The clinical success rate was maintained at follow-up; 90·7% of patients in the 200 mg moxifloxacin group, 92·8% in the 400 mg moxifloxacin group and 92·2% in the clarithromycin group, were still considered clinical successes. The 95% confidence intervals indicate that moxifloxacin is at least as effective as clarithromycin (Table 2). In the PP population at the end of therapy and follow up, the 400 mg moxifloxacin dose had a slightly higher observed cure rate than the 200 mg moxifloxacin dose, but this was not statistically significant. Thirty-one patients (11 moxifloxacin 200 mg, 10 moxifloxacin 400 mg and 10 clarithromycin) had a clinical response of failure at the end of therapy.

CLINICAL SIGNS AND SYMPTOMS

Overall, the clinical signs and symptoms of acute infection (temperature, rales/rhonchi, dullness to percussion, sputum, cough, dyspnoea, rigors/chills, haemoptysis, pleuritic chest pain, respiration rate) showed continual improvement from baseline to the end of the study treatment. There were no differences between the three treatment regimens.

BACTERIOLOGICAL RESPONSE

At baseline, pathogens were isolated from 190 of 675 patients (28%). Bacteriologically valid patients were defined as having a positive pretherapy culture and an appropriate post therapy evaluation. One hundred and twenty-eight patients (19%) constituted the bacteriologically valid population; 40 patients treated with 200 mg moxifloxacin, 47 patients with 400 mg moxifloxacin and 41 patients with clarithromycin. The predominant causative organisms were *S. pneumoniae* (53, 42%), *H. influenzae* (32, 19%), *H. parainfluenzae* (13, 10%), *M. catarrhalis* (eight, 6%), *K. pneumoniae* (six, 5%) and *S. aureus* (five, 4%).

BACTERIOLOGICAL RESPONSE BY PATIENT

The bacteriological success rate (eradication and presumed eradication) at the end of therapy and at follow-up in the PP bacteriologically evaluable population was 72·5% and 62·5%, respectively in the 200 mg moxifloxacin group, 78·7% and 53·2% (400 mg moxifloxacin) and 70·7% and 68·3% (clarithromycin). Treatment equivalence was confirmed at the end of therapy (Table 3).

BACTERIOLOGICAL RESPONSE FOR INDIVIDUAL PATHOGENS

The bacteriological success rate for the most frequently isolated organisms, at days 13–15 was 91·4% (200 mg moxifloxacin), 91·5% (400 mg moxifloxacin) and 82·9% (clarithromycin) (Table 4). The number of patients with specific organisms was generally too low to allow any firm conclusions to be drawn. However, the bacteriological success rate for *S. pneumoniae* was 95·0% (200 mg moxifloxacin), 90·5% (400 mg moxifloxacin) and 91·7%

TABLE 1. Demographic and baseline characteristics of patients (intent-to-treat population)

Characteristic	Moxifloxacin 200 mg od ($n=229$)	Moxifloxacin 400 mg od ($n=224$)	Clarithromycin 500 mg bid ($n=222$)	*P*-value
Sex				
Male	142	137	138	0·973
Female	87	87	84	
Age (mean years ± SD)	48·4 ± 20·6	48·0 ± 20·8	48·2 ± 19·2	0·974
Weight (mean kg ± SD)	67·3 ± 14·7	67·8 ± 13·5	68·0 ± 14·4	0·857
BMI (mean $kg\,m^{-2}$ ± SD)	23·6 ± 4·6	23·7 ± 4·1	24·0 ± 4·4	0·574
No. of signs and symptoms				
≤3	44	46	39	0·727
>3	185	178	183	

TABLE 2. Clinical response at end of therapy and follow-up (PP population)

Clinical response		No. of patients (%)		
		Moxifloxacin 200 mg od ($n=180$)	Moxifloxacin 400 mg od ($n=177$)	Clarithromycin 500 mg bid ($n=174$)
End of therapy	Cure	169 (93·9)	167 (94.4)	164 (94.3)
	Failure	11	10	10
		$n=161$	$n=152$	$n=153$
Follow-up	Cure	146 (90·7)	141 (92·8)	141 (92·2)
	Failure*	15	11	12

Comparison between treatment groups: differences in rates of clinical success (cure) at end of therapy and follow-up in PP population

Treatment groups	Point estimate (95% confidence interval)	
	End of therapy	Follow-up
200 mg moxifloxacin–500 mg clarithromycin	−0·2 (−5·2; 4·8)	−1·2 (−7·5; 5·2)
400 mg moxifloxacin–500 mg clarithromycin	−1·3 (−6·7; 4·1)	−2·1 (−8·6; 4·5)
200 mg moxifloxacin–400 mg moxifloxacin	−0·4 (−5·4; 4·6)	−2·1 (−8·2; 4·1)

*Clinical failures at EOT carried forward to the follow-up assessment.

TABLE 3. Bacteriological response at EOT and follow up in bacteriologically valid PP population

Bacteriological response	No. of patients (%)		
	Moxifloxacin 200 mg od ($n=40$)	Moxifloxacin 400 mg od ($n=47$)	Clarithromycin 500 mg bid ($n=41$)
End of therapy			
Bacteriological success*	29 (72·5)	37 (78·7)	29 (70·7)
Bacteriological failure†	11 (27·5)	10 (21·3)	12 (29·3)
Follow-up	$n=40$	$n=47$	$n=41$
Bacteriological success*	25 (62·5)	25 (53·2)	28 (68·3)
Missing assessments	10	16	6

Comparison between treatment groups: differences in rates of bacteriological success (cure rates) at EOT in the microbiologically valid PP population

Treatment Groups	Point Estimate (95% confidence interval)
200 mg moxifloxacin od–500 mg clarithromycin bid	1·8 (−17·9; 21·4)
400 mg moxifloxacin od–500 mg clarithromycin bid	8·0 (−10·2; 26·2)
200 mg moxifloxacin od–400 mg moxifloxacin od	−6·2 (−24·3; 11·9)

*eradication/presumed eradication; †persistence/presumed persistence/superinfection/missing assessment.

TABLE 4. Bacteriological success rate (eradication and presumed eradication) of the major pathogens to treatment with moxifloxacin and clarithromycin and their susceptibility *in vitro*

Baseline pathogen	*n*	Bacteriological success/organisms isolated at baseline (%)			
		Moxifloxacin 200 mg od	Moxifloxacin 400 mg od	Clarithromycin 500 mg bid	Median MIC pre-therapy ($mg\,l^{-1}$)
Streptococcus pneumoniae	53	19/20 (95·0)	19/21 (90·5)	11/12 (91·7)	Moxifloxacin: 0·125 Clarithromycin: 0·032
Haemophilus influenzae	32	9/9 (100·0)	13/13 (100·0)	7/10 (70·0)	Moxifloxacin: 0·032 Clarithromycin: 4·00
Haemophilus parainfluenzae	13	3/3 (100·0)	4/4 (100·0)	5/6 (83·3)	Moxifloxacin: 0·125 Clarithromycin: 32·0
Moraxella catarrhalis	8	0/1 (0·0)	4/5 (80·0)	2/2 (100·0)	Moxifloxacin: 0·064 Clarithromycin: 0·157
Klebsiella pneumoniae	6	1/2 (50·0)	1/2 (50·0)	1/2 (50·0)	Moxifloxacin: 0·125 Clarithromycin: 64·0
Staphylococcus aureus	5	—	2/2 (100·0)	3/3 (100·0)	Moxifloxacin: 0·064 Clarithromycin: 0·095

(clarithromycin) and for *H. influenzae* was 100% (200 mg and 400 mg moxifloxacin) and 70% (clarithromycin).

Bacteriological failure at the end of therapy was recorded in 11 patients treated with 200 mg moxifloxacin, 10 patients (400 mg moxifloxacin) and 12 patients (clarithromycin).

In the 200 mg moxifloxacin group, two patients had a bacteriological response of persistence (one *S. pneumoniae,* one *K. pneumoniae*), one patient, presumed persistence (*M. catarrhalis*), six patients, superinfection (one *K. pneumoniae*, one *S. pneumoniae*, two *H. parainfluenzae*, one *Enterobacter aerogenes* and one patient with *P. aeruginosa*, *Staphylococcus* spp. and *S. pneumoniae*), and two patients had missing assessments. In the 400 mg moxifloxacin group, one patient had a bacteriological response of persistence (*S. pneumoniae*), three patients, presumed persistence (one *S. pneumoniae*, one *K. pneumoniae*, one *M. catarrhalis*), four patients, superinfection (two *S. aureus*, one *H. parainfluenzae*, one *Streptococcus* spp), and two patients had missing assessments. In the clarithromycin group, two patients had a bacteriological response of persistence (one *H. influenzae*, one *H. parainfluenzae*), four patients, presumed persistence (one *S. pneumoniae*, two *H. influenzae*, one *K. pneumoniae*), two patients, superinfection (one *K. pneumoniae*, one *H. influenzae*) and four patients had missing assessments.

One patient in the clarithromycin treatment group had a reinfection with *S. pneumoniae* and one patient in the 400 mg moxifloxacin treatment group had a recurrence with *H. influenzae* at follow-up.

A bacteriological response of failure corresponded to a clinical response of failure in 10 patients: one patient in the clarithromycin group with a bacteriological response of persistence (*H. influenzae*), one patient in the 400 mg moxifloxacin group with superinfection (*S. aureus*) and all patients with presumed persistence in all three treatment groups (one, 200 mg moxifloxacin; three, 400 mg moxifloxacin and four, clarithromycin).

Infection with atypical pathogens was documented in the case of a four-fold rise or fall in antibody titres for *C. pneumoniae* or a single titre for IgM of $\geq$10 for *C. pneumoniae* and $\geq$16 for *Mycoplasma* spp. Single titres for IgG of $\geq$256 for *Legionella* spp., $\geq$512 for *C. pneumoniae* and $\leq$64 for *Mycoplasma* spp. was also excepted as documentation of infection.

Serological findings suggested the presence of atypical organisms (*Mycoplasma*, *Chlamydia*, *Legionella*, *Coxiella* spp.) in 121 of 431 patients in the PP population (28%), 37/180 treated with 200 mg moxifloxacin (20·6%), 37/177 treated with 400 mg moxifloxacin (20·9%) and 47/174 treated with clarithromycin (27·0%) (Table 5). The most frequently recorded atypical organisms were *Mycoplasma* spp. in 28/37 patients treated with 200mg moxifloxacin (76%), 25/37 patients treated with 400 mg moxifloxacin (68%) and 32/47 patients treated with clarithromycin (68%) and *Chlamydia* spp. in 15/37 patients treated with 200 mg moxifloxacin (40%), 20/37 patients treated with 400 mg moxifloxacin (54%) and 23/47 patients treated with clarithromycin (49%). Mixed infections were uncommon and the numbers too small to interpret.

In patients serologically positive for atypical infections at end of therapy, clinical cure was recorded in 94·6% patients treated with 200 and 400 mg moxifloxacin and in 93·6% of patients treated with clarithromycin. In the 200 mg moxifloxacin group, clinical cure was recorded in 26/28 patients serologically positive for a *Mycoplasma* spp. (93%) and 13/15 patients serologically positive for a *Chlamydia* spp. (87%); in the 400 mg moxifloxacin group, in 23/25 (92%) and 20/20 (100%), respectively and in the clarithromycin group, 30/32 (94%) and 21/23 (91%), respectively (Table 6).

TABLE 5. Patients serologically positive for atypical organisms

Atypical pathogen	No. of patients (%)		
	Moxifloxacin 200 mg od ($n=37$)	Moxifloxacin 400 mg od ($n=37$)	Clarithromycin 500 mg bid ($n=47$)
Mycoplasma spp.	28 (76)	25 (68)	32 (68)
Chlamydia spp.	15 (40)	20 (54)	23 (49)
Legionella spp.	0 (0)	3 (8)	4 (9)
Coxiella spp. (Q-fever)	2 (5)	1 (3)	1 (2)

TABLE 6. Clinical response of cure at end of therapy in patients serologically positive for atypical infections

Clinical cure	No. of patients (%)		
	Moxifloxacin 200 mg od	Moxifloxacin 400 mg od	Clarithromycin 500 mg bid
All atypical infections	35/37 (95)	35/37 (95)	44/47 (94)
Mycoplasma spp.	26/28 (93)	23/25 (92)	30/32 (94)
Chlamydia spp.	13/15 (87)	20/20 (100)	21/23 (91)

SUSCEPTIBILITY TESTING

Pretherapy MIC values for moxifloxacin did not exceed $1{\cdot}00\,mg\,l^{-1}$ for any of the causative pathogens tested, whereas for clarithromycin, the maximum MIC for *S. pneumoniae* was $256\,mg\,l^{-1}$, *H. influenzae* ($32\,mg\,l^{-1}$), *H. parainfluenzae* ($64\,mg\,l^{-1}$), *M. catarrhalis* ($16\,mg\,l^{-1}$) and *K. pneumoniae* ($25\,mg\,l^{-1}$).

In patients defined as bacteriological failures at end of therapy, causative organisms documented as persistent, remained sensitive to moxifloxacin: *H. influenzae* (moxifloxacin, $0{\cdot}125\,mg\,l^{-1}$; clarithromycin, $32\,mg\,l^{-1}$). *H. parainfluenzae* (moxifloxacin, $0{\cdot}064\,mg\,l^{-1}$), *K. pneumoniae* (0·25; $128\,mg\,l^{-1}$, respectively) and *S. pneumoniae* (0·125; $0{\cdot}25\,mg\,l^{-1}$, respectively). The majority of the organisms documented as causing superinfection also remained sensitive to moxifloxacin: *K. pneumoniae* (0·064–0·125; $256\,mg\,l^{-1}$), *S. pneumoniae* (0·002; 0·016–$0{\cdot}25\,mg\,l^{-1}$), *H. influenzae* (moxifloxacin, $0{\cdot}032\,mg\,l^{-1}$) and *Streptococcus* spp. (0·25; $0{\cdot}5\,mg\,l^{-1}$), however the MIC values of *S. aureus* and *H. parainfluenzae* achieved a maximum of $4\,mg\,l^{-1}$, (*S. aureus* (4; $0{\cdot}25\,mg\,l^{-1}$) and *H. parainfluenzae* (2–4; $2–4\,mg\,l^{-1}$).

SAFETY EVALUATION

Adverse events were experienced by 338 of 675 (50%) patients during the study: 113/229 patients (49%) receiving 200 mg moxifloxacin, 114/224 (51%) patients receiving 400 mg moxifloxacin and 111/222 (50%) receiving clarithromycin.

Treatment related adverse events were reported by 82/229 patients (35·8%) receiving 200 mg moxifloxacin, 84/224 patients (37·5%) receiving 400 mg moxifloxacin and 81/222 patients (36·5%) receiving clarithromycin and were mostly related to the digestive system (Table 7a). The majority of treatment related adverse events were mild or moderate in intensity and $\geq$80% in each treatment group resolved or improved.

The most frequently reported treatment related adverse events were diarrhoea in the 200 mg and 400 mg moxifloxacin groups, (5·7% and 8·5% respectively) and liver function test abnormalities in the clarithromycin group (5·9%). Liver function test abnormalities were reported with a higher frequency with 400 mg moxifloxacin (7·1%) than with 200 mg moxifloxacin (3·5%). There was no appreciable difference between the incidence of clinically significant liver function tests ($\geq 3 \times$ ULN) between the three treatment groups suggesting that the differences were not clinically important. Taste perversion was reported with a higher frequency with clarithromycin (eight patients, 3·6%) than with moxifloxacin 200 mg (three patients, 1·3%) and moxifloxacin 400 mg (two patients, 0·9%) (Table 8). No cases of phototoxicity or cases of prolongation of the QT interval were reported in any of the treatment arms.

The study drug was discontinued because of an adverse event, excluding death, in 29 patients: 7/229 patients (3%) receiving 200 mg moxifloxacin, 11/224 (5%) receiving

TABLE 7a. Summary of all adverse events (intent-to-treat population)

Adverse events (AE)	No. of patients (%)		
	Moxifloxacin 200 mg od ($n=229$)	Moxifloxacin 400 mg od ($n=224$)	Clarithromycin 500 mg bid ($n=222$)
Any adverse event (AE)	113 (49·3)	114 (50·9)	111 (50·0)
Any drug-related AE*	82 (35·8)	84 (37·5)	81 (36·5)
Any serious AE	17 (7·4)	22 (9·8)	19 (8·6)
Discontinuation because of AE†	7 (3·1)	11 (4·9)	11 (5·0)
Deaths	5 (2·2)	2 (0·9)	5 (2·3)

*Defined as events with any relationship to study drug other than 'none'.
†Excluding deaths.

TABLE 7b. Severe adverse events (intent-to-treat population) probably or possibly related to study medication

Adverse events (AE)	No. of patients (%)		
	Moxifloxacin 200 mg od ($n=229$)	Moxifloxacin 400 mg od ($n=224$)	Clarithromycin 500 mg bid ($n=222$)
Pancreatitis	1 (0.4%)	—	—
Gastrointestinal haemorrhage	1 (0.4%)	—	—
Thrombophlebitis	—	1 (0.4%)	—
Sepsis	—	1 (0.4%)	—
Pneumonia	—	1 (0.4%)	—
Respiratory acidosis	—	—	1 (0.5%)

400 mg moxifloxacin and 11/222 (5%) receiving clarithromycin. The majority of adverse events leading to discontinuation of therapy were mild to moderate in intensity and resolved after discontinuation. Adverse events leading to discontinuation of therapy were probably, possibly or remotely related to study drug treatment in five patients in the moxifloxacin 200 mg group, 11 patients in the 400 mg moxifloxacin group and five patients in the clarithromycin group and were mainly related to the digestive system.

Twelve patients (five moxifloxacin 200 mg, two moxifloxacin 400 mg and five clarithromycin) died during the study. In the clarithromycin treatment group, two deaths were considered to be possibly related to study drug treatment. The study drug was possibly responsible for the deterioration of concomitant renal disease in one patient leading to death from kidney failure; and possibly responsible for treatment failure in one patient who died from sepsis and apnoea. In the moxifloxacin 200 mg treatment group, one death was considered remotely related to study medication: the patient had a history of coronary disease and it was considered more likely that the sudden death may have been from a coronary event precipitated by pneumonia. One death in the 200 mg moxifloxacin group, was considered unassessable, although treatment failure was suggested: the patient had no history of respiratory disease, but died of respiratory failure.

Excluding deaths, 48 patients (15 moxifloxacin 200 mg, 17 moxifloxacin 400 mg and 16 clarithromycin) experienced serious or life-threatening adverse events during the study. The majority of events were unrelated to the study medication, required remedial therapy and resolved. Events that were mild to moderate and possibly or probably study drug related included lack of drug effect, diarrhoea, cerebral infarct, respiratory disorder, pleural effusion, atrial fibrillation (2) and overdose. Events that were severe and possibly or probably related to study medication included pancreatitis (1) and gastrointestinal haemorrhage (1) in the moxifloxacin 200 mg group, deep thrombophlebitis (1) and sepsis and pneumonia (1) in the moxifloxacin 400 mg group and respiratory acidosis (1) in the clarithromycin group (see also Table 7b).

CLINICAL LABORATORY TESTS

Substantial changes from baseline haematology values were observed with certain variables at endpoint within treatment groups. However, these changes were similar between

TABLE 8. The most frequently reported (in at least 2% of study population) adverse events possibly or probably related to treatment with moxifloxacin or clarithromycin

Adverse events (COSTART term)	No. of patients (%)		
	Moxifloxacin 200 mg od ($n = 229$)	Moxifloxacin 400 mg od ($n = 224$)	Clarithromycin 500 mg bid ($n = 222$)
Diarrhoea	13 (5·7)	19 (8·5)	8 (3·6)
Liver function tests abnormal	8 (3·5)	16 (7·1)	13 (5·9)
Nausea	9 (3·9)	9 (4·0)	8 (3·6)
Abdominal pain	9 (3·9)	8 (3·6)	3 (1·4)
Headache	4 (1·7)	7 (3·1)	4 (1·8)
Taste perversion	3 (1·3)	2 (0·9)	8 (3·6)
Nausea and vomiting	2 (0·9)	5 (2·2)	5 (2·3)
Vomiting	3 (1·3)	5 (2·2)	4 (1·8)
Oral moniliasis	6 (2·6)	2 (0·9)	2 (0·9)

treatment groups and may indicate changes related to CAP. Decreased leucocyte and neutrophil counts and increased eosinophil, lymphocyte, monocyte and platelet counts were recorded. Clinically significant changes were observed in leucocyte and platelet counts. No clinically relevant changes were observed in blood pressure from baseline to endpoint but a decrease in heart rate was observed in all three treatment groups compatible with recovery from pneumonia.

Changes in clinical chemistry values from baseline to endpoint were generally similar in all treatment groups and included small decreases in urea, glucose and LDH and a small increase in amylase values. Large decreases in C-reactive protein values from baseline may be a consequence of a decrease in inflammatory parameters due to control of infection. Clinically significant changes were observed in alkaline phosphatase, bicarbonate, glucose and protein values. In liver function tests in all treatment groups, small decreases were observed from baseline to endpoint in GGT [53–48 $U1^{-1}$ (200 mg moxifloxacin), 50–45 (400 mg moxifloxacin) and 51–50 (clarithromycin)], in SGOT/AST [37–26 $U1^{-1}$ (200 mg moxifloxacin), 34–28 (400 mg moxifloxacin) and 39–27 (clarithromycin)] and in alkaline phosphatase [128–118 $U1^{-1}$ (200 mg moxifloxacin), 116–109 (400 mg moxifloxacin) and 113–110 (clarithromycin)].

Discussion

This study demonstrated that moxifloxacin 200 mg or moxifloxacin 400 mg, administered orally, once daily for 10 days is no less effective in the treatment of patients with CAP, than 500 mg clarithromycin administered orally, twice daily, for 10 days. At the end of treatment all three regimens produced similar high clinical success rates (94%) which were maintained at follow-up, 21–28 days after the end of treatment, with approximately 90% of patients in each treatment arm a clinical success. By patient, the bacteriological success rate was greater for both moxifloxacin regimens (72·5%: 200 mg, 78·7%: 400mg) than for clarithromycin (70·7%). The pathogens most frequently isolated were *S. pneumoniae* (42%) and *Haemophilus influenzae* (19%). All regimens were highly successful in eradicating *S. pneumoniae*: 200 mg moxifloxacin (95·0%) was slightly more effective than clarithromycin (91·7%) and 400 mg moxifloxacin (90·5%), while moxifloxacin was 100% effective in eradicating *H. influenzae* compared to 70% with clarithromycin.

Infections with atypical organisms were successfully cured with all three treatment regimens (95%: 200 and 400 mg moxifloxacin, 94%: clarithromycin). The clinical success rate in patients serologically positive for a *Mycoplasma* spp. was similar in all three treatment arms (200 mg moxifloxacin, 93%; 400 mg moxifloxacin, 92% and clarithromycin, 94%). However, a clear benefit of treatment with 400 mg moxifloxacin over the other treatment arms was demonstrated in patients serologically positive for a *Chlamydia* spp. (200 mg moxifloxacin, 87%; 400 mg moxifloxacin, 100% and clarithromycin, 91%).

All treatment regimens were equally well tolerated; the frequency of treatment-related adverse events during the study was comparable between the treatment groups. The most frequently reported treatment related adverse events were gastrointestinal symptoms (diarrhoea, nausea and abdominal pain) in patients treated with 200 mg moxifloxacin; diarrhoea, liver function test abnormalities and nausea in patients treated with 400 mg moxifloxacin and liver function test abnormalities, gastrointestinal symptoms and taste perversion in patients treated with clarithromycin.

Particular attention was paid in this study to the adverse drug reactions specifically associated with fluoroquinolone therapy including prolongation of the QT interval (QTc), CNS events (convulsions, dizziness, sleep disturbances), hepatic reactions (transaminase elevation, hepatitis, liver failure) and phototoxicity (17). No cases of phototoxicity or QT-prolongations were reported.

The increasing prevalence of bacterial resistance to antimicrobial agents worldwide has serious implications for the treatment of CAP. Macrolide resistance has increased generally amongst penicillin susceptible and penicillin resistant strains of *S. pneumoniae* and in many countries of the world it is now more prevalent than penicillin resistance (8). This increased prevalence, independent from penicillin resistance, has brought into question the effect of macrolide usage on the development of antimicrobial resistance in *S. pneumoniae* (18). Analysis of macrolide prescribing habits and resistance patterns indicate a clear correlation over time between increased pneumococcal resistance and the increased use overall of macrolides, and particularly of the newer longer-acting macrolides, erythromycin and clarithromycin. Cross-resistance is also seen between macrolides; in practice, the development of pneumococcal resistance to erythromycin renders all other macrolides inactive against this pathogen. In France, where the prevalence of macrolide resistance is high, prescribing information for macrolides has been modified to clarify that macrolides should not be prescribed if pneumococcal pneumonia is suspected, but remain a first choice and are effective in the treatment of atypical pneumonia. Of the macrolides, erythromycin has a limited spectrum of activity and is poorly tolerated because of gastrointestinal side effects. The newer macrolides are better tolerated: azithromycin is more active *in vitro* against *Legionella* species, *H. influenzae* and *M. pneumoniae*, whereas clarithromycin is most active against *S. pneumoniae* and *C. pneumoniae* but has relatively limited *in vitro* activity against *H. influenzae* (9).

Available fluoroquinolones such as ciprofloxacin and levofloxacin yield only moderate *in vitro* activity against *S. pneumoniae* with MIC_{90}s clustering round the respective breakpoints for pneumococci ($2\,mg\,l^{-1}$) (19). However, the newer quinolones (gatifloxacin and moxifloxacin) are highly active (20). Peak MICs for moxifloxacin against *S. pneumoniae*, are at concentrations as low as 0·06–$0{\cdot}12\,mg\,l^{-1}$, irrespective of penicillin and macrolide susceptibility (21). Activity is independent of the geographic origin of the strain; those strains originating from the main foci of penicillin resistance are not different in their susceptibilities to moxifloxacin to those originating from countries with a low prevalence of penicillin resistance (22). Pulsed field gel electrophoresis (PFGE) of *S. pneumoniae* clinical isolates from the U.K. has revealed the presence of several genotypes, and analysis of penicillin binding protein (PBP) changes have shown a correlation exists between penicillin MICs and PBP alterations, however no correlation has been demonstrated between particular genotypes and levels of moxifloxacin susceptibility (23).

Recent clinical studies have demonstrated that moxifloxacin is highly efficacious in the treatment of CAP caused by typical and atypical pathogens. Clinical success at the end of therapy in a non-comparative study of 400 mg moxifloxacin once daily was 97%, and bacteriological success, 91% (24). In a comparative trial of moxifloxacin 400 mg once daily with 500 mg clarithromycin twice daily for 10 days, clinical success was 95% and bacteriological success was 96% in both treatment groups (25). In both studies there was a high prevalence of atypical pathogens: *C. pneumoniae* (54% and 47%, respectively), *M. pneumoniae* (25%, 21%), *S. pneumoniae* (12%, 17%) and *H. influenzae* (10%, 16%). In a further comparative trial of 400 mg moxifloxacin once daily with amoxicillin, 1000 g three times daily, for 10 days, the clinical success rate was 91% and 90%, respectively, and the bacteriological success rate was 90% and 83%, respectively (26). In all of these studies, including the present study, the bacteriological success rate in patients treated with 400 mg moxifloxacin from whom a penicillin resistant *S. pneumoniae* ($MIC \geq 1{\cdot}0\,mg\,l^{-1}$) was isolated was 17/18 (94%) and a clarithromycin resistant *S. pneumoniae* ($MIC \geq 8{\cdot}0\,mg\,l^{-1}$) was 26/26 (100%) (27).

A recent comparative review from published data of newer flouroquinolones in the treatment of CAP summarized that moxifloxacin 400 mg once daily and levofloxacin 500 mg once daily are microbiologically and clinically as effective as clarithromycin 500 mg twice daily, with clinical resolution in $\geq 95\%$ patients, compared to sparfloxacin 200 mg (92%) and grepafloxacin (87%) (28).

The safety profile in clinical trials has shown moxifloxacin to be generally well tolerated and safe with overall frequencies of adverse events comparable to that of the comparator regimen of B-lactams and macrolides. Moxifloxacin has shown a low propensity to cause CNS reactions (dizziness 2·9%); no potential for photosensitizing reactions; minimal, but clinically insignificant increases in QTc interval, and similar to comparators; or significant hepatic reactions. The safety profile of levofloxacin is comparable whereas a significant incidence of taste perversion (26%) and nausea (13·8%) is associated with grepafloxacin, and photosensitivity reactions with sparfloxacin (2·4%).

As moxifloxacin is not metabolized via the cytochrome P450 system the potential for interactions with comedications is low, and except for the typical absorption class interaction for quinolones with antacids and minerals, no other clinically relevant interactions have been demonstrated. Dose adjustment for renal or hepatic insufficiency is not required as moxifloxacin is excreted in a balanced fashion via renal, hepato/biliary and metabolic pathways (29,30).

The convenient once daily dosing regimen of moxifloxacin may offer an advantage in terms of improved patient compliance and thus a reduction in the likelihood of resistance selection. *In vitro* and *in vivo* experiments have demonstrated that moxifloxacin has a low propensity for selecting resistant organisms, with a spontaneous mutation frequency towards moxifloxacin in *S. pneumoniae* of 1×10^{-9}, two orders of magnitude lower than other quinolones (31).

This study indicates that moxifloxacin may have utility as an effective, well-tolerated and simple regimen in the treatment of CAP. Furthermore, the 400 mg moxifloxacin regimen is preferable over the 200 mg regimen, as higher antibacterial concentrations have a lesser propensity to induce the development of bacterial resistance (32,33) and more effectively eradicate pathogens.

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