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Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study

Thomas M. File, Jr[1]*, Lionel A. Mandell[2], Glenn Tillotson[3]†, Kosta Kostov[4] and Ognian Georgiev[5]

[1]Northeastern Ohio Universities College of Medicine, Rootstown, OH and Summa Health System, 75 Arch Street, Suite 105, Akron, OH 44304, USA; [2]McMaster University School of Medicine, 711 Concession Street, Hamilton, Ontario, L8V1C3 Canada; [3]Oscient Pharmaceuticals Corporation, 1000 Winter Street, Suite 2200, Waltham, MA 02451, USA; [4]Military Medical Academy, Pulmonary Clinic, 3 Georgi Sofijski Street, Sofia 1606, Bulgaria; [5]Alexandrovska University Multiprofile Hospital for Active Treatment, Propedeutics and Internal Diseases Department, Pulmonary Clinic, 1 Georgi Sofijski Street, Sofia 1431, Bulgaria

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***Objectives*: Short-course therapy has been advocated for the treatment of community-acquired pneumonia (CAP). We compared the efficacy and safety of 5 and 7 day courses of gemifloxacin for outpatient treatment of mild–moderate CAP.**

***Patients and methods*: In a multicentre, double-blind, parallel group study, patients were randomized to receive 320 mg of oral gemifloxacin once daily for 5 or 7 days. Over 95% of all patients in each cohort had a Fine score of ≤III. The primary efficacy endpoint was clinical cure at follow-up (days 24–30). Secondary outcomes were clinical and bacteriological responses at the end of therapy (days 7–9) and bacteriological and radiological responses at follow-up. Adverse events (AEs) were also monitored.**

***Results*: In a total of 469 per protocol (PP) patients, clinical resolution at follow-up was 95% and 92% for 5 and 7 day treatments, respectively [95% confidence interval (CI) −1.48, 7.42], indicating non-inferiority of 5 day treatment. Clinical resolution at the end of therapy was 96% for both regimens (95% CI −3.85, 3.42). Bacteriological response rates in PP patients at the end of therapy were 94% and 96% for 5 and 7 day groups, respectively (95% CI −8.27, 3.25) and 91% for both groups at follow-up (95% CI −6.89, 7.93). Radiological success in PP patients at follow-up was 98% and 93% in 5 and 7 day groups, respectively (95% CI 0.35, 7.91). Pre-therapy pathogens were identified in 242 (47.3%) patients, most commonly *Streptococcus pneumoniae*. Frequency of treatment-related AEs was 21% in both cohorts with discontinuation rates of 1.2% and 2% in the 5 and 7 day groups, respectively. A lower incidence of rash was observed in the 5 day cohort (0.4%) versus the 7 day cohort (2.8%) ($P = 0.04$).**

***Conclusions*: Gemifloxacin once daily for 5 days is not inferior to 7 days in the PP population with respect to clinical, bacteriological and radiological efficacy. Further work is needed, however, to explore whether fewer treatment days would improve patient compliance and reduce the incidence of AEs.**

Keywords: fluoroquinolones, short-course therapy, Phase III, resistance, CAP

*Corresponding author. Tel: +1-330-375-3894; Fax: +1-330-375-6680; E-mail: filet@summa-health.org
†Present address. Replidyne Pharmaceuticals, Louisville, CO, USA.

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality and is an unrelenting burden to the US healthcare system.[1] Of more than 5 million cases of CAP which occur annually in the USA, *Streptococcus pneumoniae* is the leading cause, particularly in bacteraemic and fatal episodes.[2,3] Other causative agents include *Haemophilus influenzae*, *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella* species and *Moraxella catarrhalis*, with a mixed aetiology in ~2% to 11% of all cases.[4] Approximately 80% of the patients with CAP are treated on an outpatient basis and depending on patient-associated variables, recent Infectious Diseases Society of America and American Thoracic Society guidelines recommend the use of a macrolide, either alone or in combination with a β-lactam, or a respiratory fluoroquinolone for empirical therapy.[5] However, because there are few well-controlled trials regarding the optimal duration of therapy, there has been no consensus of opinion regarding this issue, and previous guidelines recommend 7–14 days or even up to 21 days depending on the infecting organism.[6] Proponents of a shorter duration of therapy (<7 days) suggest that such a strategy would minimize the emergence of resistance, improve patient compliance and reduce treatment costs without compromising efficacy.[7–9]

Evidence of the benefits of short-course therapy (i.e. <7 days) does exist but is restricted to a few compounds and generally at higher than commonly used doses. For example, amoxicillin at a high dose (90 mg/kg) for 5 days when compared with a low dose (40 mg/kg) for 10 days was more effective in preventing carriage of resistant *S. pneumoniae* in children.[10] Likewise, levofloxacin at 750 mg for 5 days was as effective as 500 mg for 10 days,[11] but an unanswered question was whether or not the lower dose would have worked just as well for 5 days of therapy.[12] Fluoroquinolones, given their concentration-dependent killing activity, are ideal candidates to be considered for short-course CAP therapy. Gemifloxacin, like levofloxacin, is approved for use in CAP and has been shown to have greater potency *in vitro* against clinical isolates of *S. pneumoniae* when compared with other respiratory fluoroquinolones.[13] Moreover, gemifloxacin has been shown to have a favourable pharmacodynamic profile when used once daily at 320 mg.[14] At this dose, a 7 day treatment regimen with gemifloxacin proved to be as effective as 10 days of higher dose amoxicillin/clavulanate (1 g/125 mg) given three times daily for the treatment of suspected pneumococcal CAP.[15] In this study, we tested the efficacy of 320 mg once daily gemifloxacin short-course therapy for the outpatient treatment of mild-to-moderate CAP by comparing 5 and 7 day regimens.

Patients and methods

Study design and treatment

A double-blind, randomized, active controlled, parallel-group study was carried out from November 2004 to April 2005 according to the guidelines described by the Committee on the Consolidation of Standards for Reporting Trials.[16] Patients were enrolled from 68 centres in 9 countries including Bulgaria (10 centres), Croatia (2), Czech Republic (2), Lithuania (5), Poland (6), Romania (11), Russia (7), Ukraine (12) and the USA (13). The study was approved by each investigator's institutional review board and all patients gave written informed consent prior to enrolment. The primary objective was to demonstrate the non-inferiority of 5 day versus 7 day gemifloxacin with respect to clinical and bacteriological responses and to evaluate safety. Compliance was measured by the number of capsules dispensed, taken and returned for each patient. Patients were considered to be compliant if they took 100% of the intended regimen for the first 72 h (i.e. for the first three doses) and 80% of the intended regimen overall.

Patient population

The study population consisted of patients ≥18 years with a clinical diagnosis of CAP characterized by fever, radiologically confirmed evidence of new or progressive infiltrate(s) or pleural effusion consistent with pneumonia and at least two of the following signs and symptoms: new or increased cough, purulent sputum or a change in sputum characteristics, rales and/or evidence of pulmonary consolidation or dyspnoea. Patients were also evaluated for known risk factors as per CAP guidelines, which included history of cardiac conditions such as hypertension, ischaemic heart disease, congestive heart failure or other diseases known to adversely affect pneumonia outcomes (e.g. diabetes).[17] Patients were excluded from the study if they were pregnant or lactating, planning a pregnancy during the study or of child-bearing potential and not using an accepted method of contraception. Patients were also excluded if they presented with any one of the following characteristics: allergy or severe adverse reactions to carboxyquinolone derivatives, history of tendonitis while taking fluoroquinolones, severe respiratory tract infections requiring parenteral antimicrobial therapy, life-threatening or serious unstable underlying disease, hospital-acquired or aspiration pneumonia, localized bronchial obstruction, a history of post-obstructive pneumonia, cystic fibrosis, active tuberculosis, bronchiectasis, active pulmonary malignancies or the presence of a complicating infection. Patients were also excluded if they presented with disease that would compromise treatment evaluation of the study medication such as septic shock, empyema, septic arthritis, meningitis and malignancy, had evidence of significant liver (Child–Pugh class B or C) or renal impairment (creatinine clearance ≤40 mL/min), had a need for concomitant medications including sucralfate, probenecid or systemic steroids or had received previous therapy with a systemic antibiotic for more than 24 h prior to enrolment for this current episode of CAP, if they were HIV positive or otherwise immunocompromised. Patients with active alcohol or drug abuse or who were being treated with an investigational drug, vaccine or device within 30 days or 5 half-lives (whichever is longer) of study entry were also excluded.

Clinical and bacteriological evaluations

Clinical signs and symptoms were evaluated pre-therapy, during therapy (days 2–4), at the end of therapy (days 7–9) and at the follow-up visit (days 24–30). ECGs were performed prior to initiation of study drug therapy and once during therapy (days 2–4). Gram stain and sputum culture were performed at each visit. Blood cultures were performed prior to the first dose of study medication and at follow-up. Pathogens isolated were shipped to a central laboratory for confirmatory identification and susceptibility testing. Susceptibility testing was performed

according to CSLI (formerly NCCLS) guidelines.[18–20] Serological tests for *M. pneumoniae* (IFA; Wampole–Zeus Laboratories, Cranbury, NJ, USA) and *C. pneumoniae* (MIF; Focus Diagnostics, Cypress, CA, USA) were conducted on sera collected prior to the first dose of study medication and at follow-up. All testing was performed by a central laboratory (Focus Bio-Inova, Herndon, VA, USA). A urinary antigen assay for *Legionella pneumophila* (Binax-NOW, Scarborough, ME, USA) was performed prior to the first dose of study medication and patients were considered positive for *L. pneumophila* if antigen was detected. Patients were considered positive for *C. pneumoniae* or *Chlamydophila psittaci* if either organism was detected by serology and met one or more of the following criteria: there was at least a 4-fold rise in *C. pneumoniae* or *C. psittaci* IgG titre between screening and follow-up and/or there was a *C. pneumoniae* or *C. psittaci* IgM titre of $\geq$1:10 at screening and/or follow-up. Patients were considered positive for *M. pneumoniae* if IgM was detected by serology at screening and/or follow-up with an immune status ratio $\geq$1.1, either with or without a rise in *M. pneumoniae* IgG of $\geq$46% between screening and follow-up.

Clinical and bacteriological outcome definitions

The primary efficacy evaluation was clinical response (success or failure) at follow-up (visit 4, days 24–30) as per FDA regulatory guidelines.[21] Secondary efficacy outcomes included clinical and bacteriological responses at the end of therapy (days 7–9) as well as bacteriological and radiological responses at follow-up. Patients who fulfilled the inclusion and exclusion criteria, compliant with the study regimen (based on capsule count at the end of therapy visit) and attended either visit 3 (days 7–9) or visits 3 and 4 (days 24–30), constituted the clinical per protocol (PP) population. All patients who received at least one dose of study medication comprised the intent-to-treat (ITT) population. Clinical response was evaluated in this population as a secondary objective. Clinical response was based on subjective symptoms and objective signs of auscultatory findings (rales, rhonchi, wheezing and breath sounds) and was defined as success (sufficient improvement or resolution of the signs and symptoms of CAP recorded at baseline such that no additional antibacterial therapy was required at the end of therapy or follow-up), failure (insufficient improvement or deterioration of signs and symptoms of CAP such that additional antibacterial therapy was required) or indeterminate (clinical assessment was not possible). Bacteriological response was based on the results of cultures taken before and after therapy and was a secondary efficacy parameter. All patients with at least one pre-treatment pathogen were included in the bacteriological outcome evaluation, but were analysed separately as Bacteriological PP and ITT populations. New pathogens identified at the end of therapy or follow-up were categorized as new infections (clinical recurrence requiring antibacterial therapy) or colonization [not requiring therapy (clinical success)]. Success was defined as eradication or presumed eradication (if no material was available because of a clinical success or for organisms identified by serology), failure as persistence or presumed persistence (no material was available in a patient considered a clinical failure) or indeterminate (if bacteriological response to the study drug was not evaluable for any reason). For *M. pneumoniae*, *C. pneumoniae* and *C. psittaci*, because only serology was used for identification, bacteriological outcome was presumed on the basis of clinical response. Radiological outcome was based on the investigator's assessment of the posterior–anterior and lateral chest radiographs obtained at follow-up relative to baseline (pre-therapy). Success was defined as improvement or resolution of the radiological signs of CAP.

Safety and tolerability assessments

Safety was evaluated in patients who had received at least one dose of drug on the basis of physical examination findings, ECGs, adverse events (AEs), intercurrent illness and laboratory tests, including routine haematology, blood chemistry and urinalysis tests. Investigators rated each AE subjectively according to relationship with the study drug (related, possibly related and not related), severity (mild, moderate and severe) and seriousness. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Events were tabulated by type (according to the MedDRA Preferred Term and System Organ Class) and by frequency for all AEs as well as those considered related to drug.

Statistical analysis

All statistical analyses were performed using SAS®, version 8.02. The primary objective was to show that gemifloxacin treatment for 5 days was non-inferior to 7 days of treatment. Primary analysis of the clinical response at follow-up was based on the ITT and PP populations. Secondary efficacy endpoints in both the PP and ITT populations were based on clinical and bacteriological outcomes at the end of therapy and radiological and bacteriological outcomes at follow-up. For each evaluation, a two-sided 95% confidence interval (CI) for the weighted difference between treatment groups was constructed on the basis of the formula of Makuch and Simon.[22] Non-inferiority was defined as the lower limit of the two-sided 95% CI for the difference between groups being $\geq -10\%$. Assuming an underlying equivalent clinical response rate of 87.5% in the combined treatment groups at follow-up, 344 evaluable patients (172 per treatment group) were required to give a power of 80% to detect that the lower bound of the two-sided 95% CI for the difference in rates (5 day group minus 7 day group) was no less than -10%. It was anticipated that up to 25% of randomized patients would be ineligible for the PP population. Therefore, approximately 459 patients were to be recruited to provide 344 clinically evaluable patients. With this sample size, the study had a power of 80% to test the null hypothesis of non-inferiority, assuming a failure rate of 12.5% for each treatment group. All CIs for differences in proportions were calculated using the normal approximation to the binomial distribution. Comparisons of the incidence rates of AEs between the two study drug groups were performed descriptively. No interim analyses were planned or performed for this study.

Results

Patient disposition and demographic characteristics

Of 512 patients randomly assigned to receive treatment, two patients in the 7 day group were randomization failures and received no drug. The safety and ITT populations each comprised 510 patients and the PP population comprised 483 and

469 patients at the end of treatment and follow-up, respectively (Figure 1). Only 14 (2.7%) patients, including the two randomization failures, were withdrawn prematurely from the study and 10 (2%) patients completed therapy but withdrew from follow-up. AEs were the main reason for premature discontinuation, accounting for three (1.2%) and five (2%) patients in the 5 and 7 day groups, respectively. An additional three patients were excluded from the PP population as a result of poor visit compliance, treatment with another systemic antibacterial for intercurrent illnesses, poor study medication compliance or a clinical outcome of 'unable to determine'. Both treatment groups had similar baseline demographics (Table 1). The majority of patients in each arm had a Fine score of I (62% and 54% in the 5 and 7 day groups, respectively). There was a trend towards sicker patients in the 7 day group on the basis of the Fine score ($P = 0.0542$ by Mantel–Haenszel χ^2 test using rank scores). However, it is unlikely that this would make a large difference in the results as <5% of patients in each treatment group had severe pneumonia (Fine score >III; Table 1). Patients in each treatment arm were stratified retrospectively by known risk factors in accordance with recent guidelines. Approximately 22% of patients in each cohort had recognized risk factors.

Clinical outcomes

Clinical response at follow-up for the PP and ITT populations showed that a 5 day regimen of gemifloxacin was non-inferior to a 7 day regimen for the treatment of mild–moderate CAP. In the PP population, 230 (95.0%) patients in the 5 day group and 209 (92.1%) patients in the 7 day group had a clinical response of success at follow-up (Table 2). In the ITT population, 237 (92.6%) patients in the 5 day group and 221 (87.0%) in the 7 day group had a clinical response of success (Table 2). Logistic regression analysis revealed a statistically significant advantage for the 5 day regimen over the 7 day regimen in the ITT population ($P = 0.041$), but no significant difference between treatments in the PP population ($P = 0.207$) (Table 2). No treatment-by-country interaction was noted. Radiological success at follow-up in both populations was also comparable for each treatment arm (Table 2). Approximately 96% of

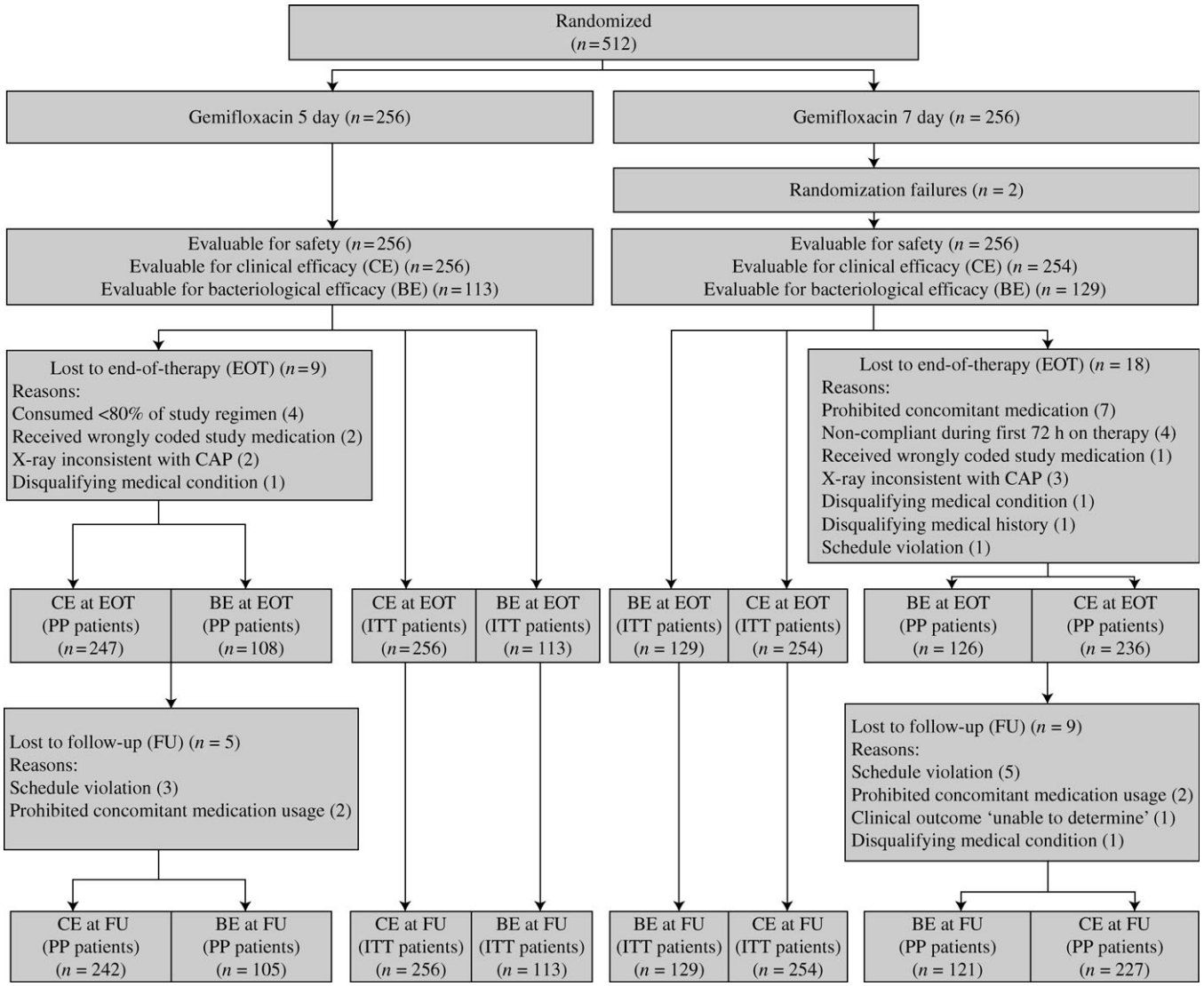

Figure 1. Populations analysed for 5 day and 7 day treatment with gemifloxacin.

Table 1. Demographics and baseline characteristics of ITT population

Characteristic	Treatment group	
	5 day ($N = 256$)	7 day ($N = 254$)
Age (years)		
mean (SD)	44.9 (16.4)	45.9 (17.3)
range	18–80	18–98
Sex, *n* (%) male	146 (57)	148 (58)
Race, *n* (%) Caucasian	254 (99)	251 (99)
History of cigarette smoking, *n* (%)		
current smoker	75 (29.3)	84 (33.1)
former smoker	31 (12.1)	37 (14.6)
non-smoker	150 (58.6)	133 (52.4)
Risk factors, *n* (%)[a]		
age $\geq$ 65	41 (16)	41 (16.1)
diabetes	13 (5.1)	12 (4.7)
COPD	10 (3.9)	5 (2)
CHF	5 (2)	4 (1.6)
CVD	5 (2)	4 (1.6)
other[b]	36 (14.1)	23 (9.1)
CAP severity[c], *n* (%)		
I	158 (61.7)	136 (53.5)
II	72 (28.1)	85 (33.5)
III	22 (8.6)	21 (8.3)
IV	3 (1.2)	11 (4.3)
V	1 (0.4)	1 (0.4)

N, total number of patients; *n*, number of patients with characteristic. Abbreviations: COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CVD, cerebral vascular disease.
[a]Some patients may have more than one risk factor.
[b]Includes myocardial infraction, hypertension, cardiomyopathy, atrial fibrillation, congenital heart disease, heart failure, ischaemic cardiomyopathy, cerebral infarct and coronary heart disease alone or in combination.
[c]Graded using Fine criteria.[23,24]

patients in each treatment group in the PP population had a clinical response of success at the end of the therapy. Results were similar for the ITT population.

Among patients with at least one risk factor, 50/55 (90.9%) in the 5 day group and 51/55 (92.7%) in the 7 day group had a clinical response of success at follow-up. One hundred eighty-seven (93%) patients without risk factors in the 5 day group and 170 (85.4%) in the 7 day group had a successful response. Owing to the low incidence of clinical failures, it was not possible to identify trends related to treatment failure in either group.

Bacteriological outcomes

Bacteriological response rates were similarly high in the PP and ITT populations at the end of therapy as well as at follow-up. However, non-inferiority for 5 day treatment was only noted in the PP population at the end of therapy (Table 2). Clinical response in the Bacteriological PP population was also assessed and success was observed in 93% and 94% of patients in the 5 and 7 day groups, respectively. Of the total 242 (47.3%) patients identified with a pre-therapy pathogen, 159 (66%) had a single pathogen and 58 (24%) had two pathogens identified. The treatment groups were similar in the number of pathogens isolated at pre-therapy. *S. pneumoniae*, the most common pathogen found, was isolated from 68 patients (28%), of which 26 (23%) and 42 (33%) were in the 5 and 7 day groups, respectively. Multidrug-resistant *S. pneumoniae* (MDRSP) was identified in five and six patients in the 5 and 7 day groups, respectively. The other most common pathogens identified pre-therapy were *C. pneumoniae* (53 patients, 22%), *M. pneumoniae* (48 patients, 20%), *H. influenzae* (42 patients, 17%) and *Staphylococcus aureus* (non-MRSA; 42 patients, 17%). A similar pathogen profile was observed for the Bacteriological PP population. Eradication rates were comparable in both treatment groups in the Bacteriological PP population (Table 3). Eradication rates for *S. pneumoniae* at the end of therapy and at follow-up were 100% for the 5 day group (including five of five patients with MDRSP) and 95% for the 7 day group at the end of therapy

Table 2. Success rates for PP and ITT populations at end of therapy and follow-up

			Treatment group				
			5 day		7 day		
	Population	Response	*n/N*	%	*n/N*	%	95% CI for difference[a]
End of therapy	PP	clinical	236/247	95.5	226/236	95.8	−3.85, 3.42
		bacteriological	101/108	93.5	121/126	96	−8.27, 3.25
	ITT	clinical	240/256	93.8	234/254	92.1	−2.82, 6.07
		bacteriological	104/113	92	124/129	96.1	−10.09, 1.91
Follow-up	PP	clinical	230/242	95	209/227	92.1	−1.48, 7.42
		bacteriological	96/105	91.4	110/121	90.9	−6.89, 7.93
		radiological	236/242	97.5	212/227	93.4	0.35, 7.91
	ITT	clinical	237/256	92.6	221/254	87	0.34, 10.81
		bacteriological	101/113	89.4	115/129	89.1	−7.58, 8.05
		radiological	243/256	94.9	225/254	88.6	1.59, 11.09

N, total number of patients; *n*, number of patients with clinical, bacteriological or radiological success.
[a]Based on the normal approximation to the binomial distribution. The lower confidence limit $\geq -10\%$ indicates non-inferiority.

Table 3. Eradication rates for major pre-pathogens in the PP population

	Treatment group			
	5 day		7 day	
Pathogen	*n/N*	%	*n/N*	%
Follow-up				
Streptococcus pneumoniae	26/26	100	34/40	85
Haemophilus influenzae	21/22	95.5	18/18	100
Chlamydia pneumoniae	17/18	94.4	30/31	96.8
Mycoplasma pneumoniae	22/25	88	19/20	95
Staphylococcus aureus	13/15	86.7	21/23	91.3
End of therapy				
S. pneumoniae	26/26	100	40/42	95.2
H. influenzae	22/23	95.7	19/19	100
C. pneumoniae	18/19	94.7	31/32	96.9
M. pneumoniae	24/26	92.3	20/20	100
S. aureus	13/15	86.7	24/25	96

N, number of isolates obtained; *n*, number of patients with eradication or presumed eradication, based on clinical response.

Table 4. Treatment emergent AEs

	Treatment group		
Adverse event	5 day ($N = 256$) *n* (%)	7 day ($N = 254$) *n* (%)	total ($N = 510$) *n* (%)
ALT elevated[a]	19 (7.4)	12 (4.7)	31 (6.1)
AST elevated	19 (7.4)	7 (2.8)	26 (5.1)
Diarrhoea	9 (3.5)	7 (2.8)	16 (3.1)
Loose stool	3 (1.2)	3 (1.2)	6 (1.2)
Nausea	3 (1.2)	2 (0.8)	5 (1)
Headache	3 (1.2)	5 (2.0)	8 (1.6)
Dizziness	3 (1.2)	4 (1.6)	7 (1.4)
Hyperglycaemia	1 (0.4)	3 (1.2)	4 (0.8)
Rash	1 (0.4)	7 (2.8)	8 (1.6)
Upper abdominal pain	1 (0.4)	2 (0.8)	3 (0.6)

N, total number of patients; *n*, number of patients experiencing event.
[a]The basis for the trend of increased incidence of ALT elevations in the 5 day group is due to higher baseline ALT levels in those randomized to this group versus the 7 day group. ANCOVA and logistic regression analyses support this trend.

(including four of six patients with MDRSP). Similar eradication rates were noted in the Bacteriological ITT population (data not shown). MICs of gemifloxacin did not exceed 0.03 mg/L for any of the pathogens isolated.

There was only one patient enrolled who had *Legionella* identified as a cause of CAP (a patient randomized to the 5 day group). For this patient, there was also a 4-fold rise in antibody titres for both *Chlamydophila* and *Mycoplasma*; thus, this may have represented a mixed 'atypical' pneumonia. The clinical response for this patient at follow-up was considered to be unsuccessful. There were three cases of clinical failures associated with persistence of the originally isolated pathogen. Of these, two were in the 5 day group (*Klebsiella pneumoniae* and *S. pneumoniae*) and one was in the 7 day group (*S. aureus*).

Safety and tolerability

Treatment-related AEs occurring either during therapy or within 30 days post-therapy were reported for 21% of patients in each treatment group. Discontinuation of the study drug in the ITT population due to AEs occurred infrequently: 3/256 (1.2%) and 5/254 (2%) for the 5 and 7 day cohorts, respectively. All patients had ECG readings within the acceptable range. No patient had treatment discontinued because of rash as an AE. The most frequently reported treatment-related AEs were elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were higher in the 5 day group (ALT and AST each 7.4%) when compared with the 7 day group (ALT 4.7% and AST 2.8%) (Table 4). The evaluation of ALT laboratory values at baseline showed that the incidence of elevated serum ALT was higher in the 5 day group (12%) than in the 7 day group (6%). Adjusting for this imbalance via ANCOVA and logistic regression analyses, ALT elevations during the therapy and at the end of therapy visits were significantly associated ($P<0.001$) with elevated baseline ALT levels, whereas the association with a particular treatment group was non-significant. The mean ALT on therapy/baseline ratio was low in both groups (1.17 for 5 days and 1.15 for 7 days). Other treatment-related AEs occurring with a frequency of >2% in either cohort included diarrhoea (3.5% and 2.8% for the 5 and 7 day cohorts, respectively) and rash. As revealed by χ^2 analysis, the incidence of rash was significantly lower in the 5 day group, occurring in only one (female; 0.4%) patient when compared with seven (three males and four females; 2.8%) patients in the 7 day group ($P = 0.04$). The single event of mild, non-serious rash in the 5 day group was short-lived, lasting only 3 days, and it occurred 2 days after completion of drug treatment. In the 7 day group, all rashes were non-serious in intensity (two mild, three moderate and two severe) and all but two occurred after completion of study treatment. The incidence of rash was higher in patients under 40 years of age (3%), compared with those over 40 (1%). Serious AEs (including 1 death) were reported for 8 (3%) and 14 (6%) patients in the 5 and 7 day groups, respectively. The death of a male patient (7 day group) due to a myocardial infarction occurred during treatment and was considered unrelated to the study drug. The patient's medical history included type II diabetes mellitus since 1985 and arterial hypertension since 2002 but had no prior history of myocardial infarctions. The patient was assessed as a clinical success with respect to CAP signs and symptoms. Of the serious AEs, only three (7 day group) including acute renal failure, gastritis and ventricular extrasystoles were considered to be possibly related to study medication.

Discussion

An effective short-course antibiotic regimen for CAP has the potential to decrease the incidence of AEs, to increase patient compliance, to decrease costs and to reduce the selection pressure for antibiotic resistance. In this study, 320 mg of

gemifloxacin once daily for 5 days was non-inferior to 7 days in terms of clinical success and eradication of major pathogens.

The clinical resolution at follow-up was 95% and 92% for 5 and 7 day treatments, respectively (95% CI −1.48, 7.42), indicating non-inferiority of 5 day treatment. Clinical resolution at the end of therapy was 96% for both regimens (95% CI −3.85, 3.42). Bacteriological response rates in PP patients at the end of therapy were 94% and 96% for 5 and 7 day groups, respectively (95% CI −8.27, 3.25) and 91% for both groups at follow-up (95% CI −6.89, 7.93). The observation that the bacteriological outcome rate (96.1%) was slightly better than clinical success (92.1%) in the 7 day group at the end of therapy is interesting because the clinical outcome is often similar or exceeds the bacteriological success rate. There was no definite explanation for this observation. One hundred percent eradication of *S. pneumoniae* including MDRSP was noted both at follow-up and end of therapy in the 5 day group. These results confirm that gemifloxacin when given for 5 days can be used with confidence to treat CAP empirically with excellent coverage for the most common causative organisms.

The incidence of AEs was low in this study and both gemifloxacin regimens were well tolerated. The proportion of discontinuations due to AEs was 1.2% and 2% for the 5 and 7 day groups, respectively. These rates compare favourably with those of other fluoroquinolones. In a recent, open-label Phase IV study of the efficacy and safety of levofloxacin in 'real world' patients with CAP, the rate of discontinuations due to at least one AE was 4.4%.[25] Similarly, in a review of the safety profile of moxifloxacin, the rate of discontinuations due to a drug-related AE was also 4%.[26] The most frequently reported treatment-related AEs in the present study were increased levels of ALT and AST. However, when adjusted for baseline levels (prior to therapy), there was no statistical difference between the 5 and 7 day treatment groups. In addition, no patient with elevated liver enzymes exhibited any clinical signs of hepatic toxicity. Furthermore, abnormal liver function tests are not uncommon in patients with CAP.[27] The only other AEs to occur with a frequency of >2% in either cohort were diarrhoea and rash. Rash occurred with a lower frequency in the 5 day group (0.4% versus 2.8% in the 7 day group) and was never a cause for the discontinuation of treatment. These data are consistent with previous clinical experience with gemifloxacin that the incidence of rash is lower with shorter duration of therapy.[28] No serious treatment-related AEs were reported for 5 day patients when compared with three serious treatment-related AEs in the 7 day group. Thus, it would appear that shorter course therapy may limit the incidence of serious drug-related AEs. However, further work is needed to substantiate this finding.

Approximately 22% of the patients in each cohort had comorbidities (Table 1) and consequently met criteria for being at risk of a poorer outcome.[5,24] However, patients receiving 5 days of therapy had similar clinical success rates as those receiving the 7 day treatment, despite the presence of these known risk factors. A potential limitation of the study is that there was a trend towards sicker patients in the 7 day group based on the Fine score ($P = 0.0542$ by Mantel–Haenszel χ^2 test using rank scores). However, it is unlikely that this would make a large difference in the results as <5% of patients in each treatment group had severe pneumonia (Fine score >III; Table 1). Owing to the low incidence of clinical failures, it was not possible to identify any trends related to treatment failure in either group. These data support the use of 5 day gemifloxacin therapy in the treatment of mild-to-moderate CAP, including patients with co-morbidities.[7,29]

The efficacy of short-course therapy for CAP has been demonstrated previously with azithromycin,[30,31] amoxicillin,[32] telithromycin[33] and levofloxacin.[11] In a recent study of hospitalized patients with mild-to-moderate CAP (mostly Fine scores ≤III as in the present study), patients randomized to 3 days of intravenous amoxicillin alone (750 mg three times daily) showed clinical success similar to those subsequently switched to oral amoxicillin for 5 more days.[32] However, there was a non-statistically significant increase in AEs in the 8 day group. In another study, a 750 mg dose of levofloxacin once daily for 5 days was found to be as effective as 500 mg for 10 days.[11] In this study, it was not possible to determine the effectiveness of short-course therapy alone because two different doses were studied.[12] In the present study in which the only variable was duration of therapy, we clearly demonstrated that the standard 320 mg dose of gemifloxacin is effective for 5 days.

Short-course antibiotic therapy has also been shown to aid in suppressing the development of resistance. A randomized trial of short-course, high-dose amoxicillin treatment in children showed a statistically significant decrease in carriage of penicillin-resistant *S. pneumoniae* (PRSP) and further showed that adherence to treatment was higher in the short-course, high-dose group (82% versus 74%; $P = 0.02$).[10] Similarly, another study in children confirmed that a longer duration of β-lactam treatment at a lower daily dose promotes pharyngeal carriage of PRSP.[34] An advantage of gemifloxacin is its potent antimicrobial activity at concentrations achievable in respiratory tissues and its low propensity to select for resistance.[35] With short-course gemifloxacin therapy, concerns about the emergence of resistance could be diminished; however, further work is needed.

In summary, this study has shown that oral gemifloxacin 320 mg once daily for 5 days is effective clinically, bacteriologically and radiologically in the treatment of patients with mild-to-moderate CAP, including those having known risk factors. Furthermore, the shorter exposure of patients to gemifloxacin therapy may also minimize the number of adverse drug reactions such as rash.

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