Randomized, Open-Label, Parallel-Group, Multicenter Study of the Efficacy and Tolerability of IV Gatifloxacin with the Option for Oral Stepdown Gatifloxacin Versus IV Ceftriaxone (With or Without Erythromycin or Clarithromycin) with the Option for Oral Stepdown Clarithromycin for Treatment of Patients with Mild to Moderate Community-Acquired Pneumonia Requiring Hospitalization

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ABSTRACT

Background: Empiric therapy for community-acquired pneumonia (CAP) requires the use of antibiotics with activity against a broad spectrum of respiratory pathogens and suitable pharmacokinetic properties to simplify IV-to-oral stepdown therapy switches.

Objective: The aim of this study was to compare the efficacy and tolerability of IV gatifloxacin with the option for oral stepdown gatifloxacin with a standard regimen of IV ceftriaxone (with or without erythromycin or clarithromycin) with the option for oral stepdown clarithromycin in patients with mild to moderate CAP requiring hospitalization.

Accepted for publication March 4, 2003.
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Methods: In a randomized, open-label, parallel-group, multicenter study, adults with CAP received 7 to 14 days of treatment with either IV gatifloxacin 400 mg QD with the stepdown option or IV ceftriaxone 1 or 2 g QD (with or without erythromycin 0.5 or 1 g QID or clarithromycin 500 mg BID) with the stepdown option.

Results: One hundred seventy adults with CAP were included in the study. IV gatifloxacin was stepped down to oral gatifloxacin in 90.6% (77/85) of patients; IV ceftriaxone was stepped down to oral clarithromycin in 87.1% (74/85) of patients. Among clinically evaluable patients (n = 153), cure rates at 1 to 3 days after treatment were 97.4% in the gatifloxacin group (74/76) and 90.9% in the ceftriaxone group (70/77), with a 95% CI for the difference (–3.7% to 19.1%) indicating statistical equivalence. In patients in whom pathogens were isolated from pretreatment sputum cultures, bacteriologic eradication rates were 100.0% (29/29) and 90.9% (30/33), respectively. Both regimens were well tolerated; treatment-related adverse events occurred in 27.1% (23/85) and 21.2% (18/85) of patients, respectively.

Conclusions: In the population studied, treatment with IV gatifloxacin with an option for oral stepdown gatifloxacin was as effective for achieving clinical cure as IV ceftriaxone (with or without concomitant IV erythromycin or clarithromycin) with an option for oral stepdown clarithromycin. Both regimens were well tolerated. (*Clin Ther.* 2003;25:1453–1468)

Key words: gatifloxacin, ceftriaxone, clarithromycin, erythromycin, community-acquired pneumonia, tolerability.

INTRODUCTION

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in adults. In the United States, the combined category of pneumonia and influenza is the sixth most common cause of death.[1] Although mortality rates are low (1% to 5%) among CAP patients who can be managed on an outpatient basis, they increase dramatically (≤21%) in hospitalized patients, who often are more ill and/or have a greater number of comorbid conditions.[2] During the past decade, the emergence of antibiotic-resistant strains among the common causative organisms, particularly *Streptococcus pneumoniae*,[3] has made effective treatment of CAP increasingly difficult. This has provided the impetus for the use of empiric antibiotic regimens that have good activity against *S pneumoniae* and other common causative organisms, including *Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis,* and the atypical pathogens *Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *Legionella pneumophila.* For over a decade, the guidelines of the Infectious Diseases Society of America (IDSA)[1] and the

American Thoracic Society (ATS)[4] have recommended ceftriaxone with or without a macrolide as initial empiric therapy for treatment of hospitalized patients with CAP. However, the IDSA and ATS also recommend the use of fluoroquinolones with expanded pneumococcal activity in geographic areas where resistance is prevalent.[1,4] These guidelines are recognized by the Associação Latino-Americana de Tórax[5] and other medical associations around the world.

Newer generation fluoroquinolone antibiotics, which have enhanced activity against gram-positive organisms (including resistant *S pneumoniae*) compared with older fluoroquinolones (eg, ciprofloxacin, fleroxacin, and ofloxacin),[6–8] are increasingly used as empiric monotherapy for CAP. In addition to having good activity against the common causative organisms, the newer fluoroquinolones exhibit high pulmonary tissue penetration and have good oral bioavailability,[8] permitting IV-to-oral stepdown therapy switches with the same agent—an important strategy in the management of CAP patients because it allows early hospital discharge.[9,10]

Gatifloxacin, a newer 8-methoxyfluoroquinolone compound, has potent gram-positive activity while retaining broad-spectrum activity against gram-negative pathogens. Gatifloxacin has minimal inhibitory concentrations against *S pneumoniae* (including both penicillin-susceptible and penicillin-resistant strains), *S aureus,* and the atypical pathogens *C pneumoniae, M pneumoniae,* and *L pneumophila* that are 4 to 8 times lower than those of ciprofloxacin and ofloxacin.[11] Gatifloxacin has a long elimination half-life (6 to 8 hours), making it suitable for once-daily administration, and very high oral bioavailability (almost 100%), which allows patients to be switched from IV to oral therapy without dosage adjustment.[12] Studies in CAP patients have shown that gatifloxacin produces clinical cure rates ranging from 87% to 98%, and it has been demonstrated to be as effective as comparator antibiotics, such as clarithromycin and levofloxacin.[13,14]

In this study, we investigated the comparative efficacy and safety of IV gatifloxacin with the option for stepdown to oral gatifloxacin and a standard regimen of IV ceftriaxone (with or without IV erythromycin or clarithromycin to provide cover against possible atypical pathogens[1,4]) with the option for stepdown to oral clarithromycin for 7 to 14 days in adults with mild to moderate CAP[1] requiring hospitalization.

PATIENTS AND METHODS

A randomized, open-label, parallel-group study was undertaken at 21 sites in 5 countries (Argentina, 4 centers; Australia, 1; Brazil, 5; Mexico, 7; and Thailand, 4) between October 1999 and October 2000. The study was conducted in accordance with the informed consent guidelines in the US Code of Federal Regulations[15,16] and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before any protocol-related procedures were initiated.

Patients and Medications

Patients (aged ≥18 years) with clinical evidence of mild or moderate CAP that, in the opinion of the investigator, required hospitalization were enrolled in the study. Assessment of patients was guided by the ATS guidelines for initial management of adults with CAP.[4] In each case, the diagnosis was confirmed by the presence of new infiltrate(s) on a chest radiograph and ≥2 of the following: fever >38°C (axillary); leukocytosis (>10,000 leukocytes/mm^3 or >15% bands); cough; chest pain; purulent sputum (>25 polymorphonuclear leukocytes [PMNs] and <10 squamous epithelial cells per low–power field); Gram's stain revealing neutrophils and a predominant pathogen suspected by smear of transtracheal aspirate, bronchial brushings, or biopsy material; identification of a predominant pathogen on Gram's stain of direct lung aspirate; and auscultatory findings (eg, rales, egophony).

Patients were ineligible for enrollment for any of the following reasons: (1) need for intubation and ventilation; (2) terminal illness or rapidly progressive underlying disease; (3) condition that mimics or complicates the infectious process (eg, known bronchial obstruction, history of postobstructive pneumonia, cystic fibrosis, active pulmonary malignancy); (4) known or suspected active tuberculosis, empyema, or pulmonary infection with fungi, parasites, or viruses; (5) immune function disorder; (6) renal insufficiency; (7) malabsorption syndrome; or (8) pregnancy and/or lactation. Patients were also ineligible if they had received a systemic antibiotic ≤14 days before enrollment (unless the drug was deemed ineffective for the treatment of CAP) or if they were currently receiving long-term (≥2 weeks) systemic corticosteroid therapy at a dosage >10 mg/d of prednisone (or equivalent) or terfenadine, astemizole, or cisapride.

Following the pretreatment/screening assessment—which included a complete physical examination, measurement of vital signs, clinical evaluation of the signs and symptoms of CAP, a chest radiograph, macroscopic assessment, Gram's stain and routine culture of respiratory secretions (if available), 2 specimens for blood culture, and blood and urine specimens for laboratory and pregnancy testing—eligible patients were randomly assigned to treatment with 1 of 2 regimens for 7 to 14 days. One group received IV gatifloxacin* 400 mg QD administered over 60 minutes. After the first 2 days, at the discretion of the investigator, patients could be switched to oral gatifloxacin 400 mg QD for the remainder of the study treatment period. The other group received IV ceftriaxone† 1 or 2 g (determined by the investigator) QD over 60 minutes. When infection with an atypical pathogen (eg, *L pneumophila, M pneumoniae, C pneumoniae*) was suspected, either erythromycin lactobionate‡ 0.5 or 1 g (determined by the investigator) IV QID or, in Argentinean centers only (where IV erythromycin was unavailable), IV clarithromycin§ 500 mg BID was also given over 60 minutes. After the first

*Trademark: Tequin® injection (Bristol-Myers Squibb Company, Princeton, New Jersey).
†Trademark: Rocephin® for injection (Roche Pharmaceuticals, Nutley, New Jersey).
‡Trademark: Erythrocin® lactobionate (Abbott Laboratories Inc., Abbott Park, Illinois).
§Trademark: Klaricid©, marketed in the United States as Biaxin® (Abbott Laboratories Inc.).

2 days, at the discretion of the investigator, patients could be switched to oral clarithromycin 500 mg BID for the remainder of the study treatment period.

All patients were reassessed while receiving treatment (between days 2 and 4), 1 to 3 days after the cessation of treatment, or before the start of any other antimicrobial therapy (end-of-treatment/test-of-cure visit), as well as 7 to 14 days after the cessation of treatment (posttreatment/follow-up visit). At each of these assessments, the procedures undertaken at the pretreatment visit were repeated and patients were assessed for adverse events and compliance with oral medication regimens.

Efficacy Assessment

Clinical and bacteriologic responses were determined from data obtained at the end-of-treatment/test-of-cure visit in clinically evaluable patients (ie, those who received at least 5 days of therapy [or 3 days in the case of treatment failure]). The clinical response was rated as *cured* (resolution or improvement of all signs and symptoms, except cough, such that no further treatment was required), *failure* (progression of primary signs and symptoms, development of new findings consistent with pneumonia, or death due to pneumonia), or *unable to determine* (absence of end-of-treatment data or administration of another antibiotic with activity against the pathogen involved). In microbiologically evaluable patients (ie, clinically evaluable patients in whom a bacterial pathogen susceptible to the study drugs was isolated from a pretreatment sputum culture), bacteriologic responses were rated as *eradicated, presumed eradicated* (patient not producing sputum but clinically cured), *persistent, presumed persistent* (patient not producing sputum but a clinical failure), or *unable to determine*.

At the posttreatment/follow-up visit, patients who were considered cured at the earlier test-of-cure visit were evaluated for the occurrence of relapse or new infections.

Safety Assessment

Safety was assessed via reports of adverse events recorded in the patients' clinical report forms (irrespective of causality), physical examination findings, vital sign measurements, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). Data for the safety assessments were collected between 1 and 30 days after the last treatment day.

Statistical Analysis

Demographic and pretreatment characteristics were summarized for each treatment group. These summaries included means, standard deviations, and medians for continuous data and frequency count for categoric variables.

Based on an estimated 80% clinical cure rate for patients with CAP treated with ceftriaxone, 112 evaluable patients per arm would yield an 80% power to claim that the cure rate for the gatifloxacin arm was ≤15% lower than the cure rate for

the ceftriaxone arm (α = 0.05, 2-sided). Assuming this cure rate and an 80% evaluability rate, the necessary sample size was calculated to be 280 patients with 140 patients per treatment arm.

For the primary efficacy assessment (ie, the clinical response at the end-of-treatment/test-of-cure visit), 95% CIs for the difference in cure rates (gatifloxacin minus ceftriaxone) were constructed for both clinically evaluable patients and all treated patients. Gatifloxacin was considered equivalent to ceftriaxone (with or without erythromycin or clarithromycin) if either of the following conditions was observed: (1) the larger of the 2 observed cure rates was ≥90% and the lower CI was ≤10%; or (2) the larger of the 2 observed cure rates was ≥80% and <90% and the lower CI was ≥15%. In addition, bacteriologic eradication rates were summarized for microbiologically evaluable patients, and safety data were summarized and tabulated with descriptive statistics for all patients who received ≥1 dose of the study drugs.[17]

RESULTS

Patient accrual was stopped after 170 patients were randomized because of better-than-expected clinical response for both the gatifloxacin and ceftriaxone arms. A total of 140 of the 170 enrolled patients (82.4%) were from Latin America: Mexico (n = 45), Brazil (n = 56), and Argentina (n = 39). In addition, 153 patients (gatifloxacin, n = 76; ceftriaxone, n = 77) were evaluable for clinical efficacy. The majority of the 17 patients considered unevaluable lacked an end-of-treatment evaluation or received >1 dose of another antibiotic before or during treatment (protocol violations). The microbiologically evaluable population in whom pretreatment pathogens were isolated comprised 62 patients (gatifloxacin, n = 29, ceftriaxone, n = 33), some of whom had >1 identified pathogen. The most commonly occurring pathogens were *H influenzae, S pneumoniae, S aureus,* and *M catarrhalis.* In some cases, respiratory specimens were not available or did not meet evaluability criteria (eg, low leukocyte count, no predominant organism).

As shown in Table I, the 2 patient groups had similar baseline characteristics. The typical enrolled patient had 3 or 4 signs and symptoms consistent with CAP. Most patients in both groups received 7 to 14 days of treatment with the study medications (84.7% of the gatifloxacin group [72/85] vs 91.8% of the ceftriaxone group [78/85]). A total of 90.6% of the gatifloxacin group (77/85) received IV therapy (median duration, 3 days) followed by oral stepdown gatifloxacin; 87.1% of the ceftriaxone group (74/85) received IV therapy (median duration, 4 days) followed by oral stepdown clarithromycin. Of patients in the ceftriaxone group, 36.5% (31/85) also received IV erythromycin or clarithromycin for a suspected atypical pathogen.

Clinical Response Rates

As shown in Table II, among clinically evaluable patients, the cure rate was 97.4% in the gatifloxacin group (74/76) and 90.9% in the ceftriaxone group

(70/77). The 95% CI for the difference (–3.7% to 19.1%) is consistent with the statistical equivalence of the 2 regimens. In the clinically evaluable population, 2 patients who received gatifloxacin (2.6%) and 7 who received the ceftriaxone regimen (9.1%) were classified as treatment failures. Most commonly, failure was associated with persistence or worsening of the primary signs and symptoms of

Table I. Demographic and clinical characteristics of 170 patients randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD (n = 85) or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID (n = 85). All values except age are given as number (%) of patients.

Characteristic	Gatifloxacin Group	Ceftriaxone Group
Age, y		
Mean	57.3	57.5
Range	18–91	17–90
Sex, no. (%)		
Women	46 (54.1)	47 (55.3)
Men	39 (45.9)	38 (44.7)
Race		
Hispanic	33 (38.8)	27 (31.8)
White	32 (37.6)	34 (40.0)
Asian	14 (16.5)	16 (18.8)
Black	4 (4.7)	7 (8.2)
Other	2 (2.4)	1 (1.2)
Pretreatment signs and symptoms		
Cough	83 (97.6)	82 (96.5)
Rales	71 (83.5)	68 (80.0)
Sputum production	70 (82.4)	74 (87.1)
Dyspnea	64 (75.3)	49 (57.6)
Chest pain	60 (70.6)	54 (63.5)
Fever	58 (68.2)	59 (69.4)
Pretreatment pathogen(s)		
Patients with pathogens	26 (30.6)	32 (37.6)
Pathogens isolated*		
Haemophilus influenzae	13 (15.3)	15 (17.6)
Streptococcus pneumoniae	10 (11.8)	7 (8.2)
Staphylococcus aureus	7 (8.2)	6 (7.1)
Moraxella catarrhalis	1 (1.2)	4 (4.7)
Other bacteria†	2 (2.4)	5 (5.9)

(continued)

Table I. (Continued)

Characteristic	Gatifloxacin Group	Ceftriaxone Group
Pneumonia episode within previous 12 months		
Chest radiographic findings	7 (8.2)	6 (7.1)
Single-lobe involvement	56 (65.9)	59 (69.4)
Unilateral multilobe involvement	12 (14.1)	7 (8.2)
Bilateral involvement	17 (20.0)	19 (22.4)
Preexisting medical conditions		
Cardiovascular conditions	34 (40.0)	26 (30.6)
Head, eye, ear/nose/throat disorders	20 (23.5)	19 (22.4)
Gastrointestinal disorders	17 (20.0)	20 (23.5)
Endocrine/metabolic conditions	12 (14.1)	17 (20.0)
Other pulmonary diseases	27 (31.8)	32 (37.6)

*A total of 33 pathogens were identified in the gatifloxacin group and 37 in the ceftriaxone group; some patients had >1 pathogen.

†*Streptococcus pyogenes, Acinetobacter baumannii, Enterobacter cloacae, Providencia rettgeri,* and *Acinetobacter calcoaceticus.*

pneumonia (gatifloxacin, n = 2; ceftriaxone, n = 5), but new signs or symptoms of pneumonia occurred in 2 patients in the ceftriaxone group. One of the gatifloxacin patients and 2 of the ceftriaxone patients subsequently died.

Clinical cure among microbiologically evaluable patients occurred in 100.0% of patients receiving gatifloxacin (29/29) and 87.9% of patients receiving ceftriaxone (29/33). Clinical cure rates by pathogen for gatifloxacin and ceftriaxone are shown in Figure 1.

Analysis of the clinical response rate according to the presence or absence of various prognostic factors showed that all 9 patients who failed treatment were aged >65 years (Figure 2). A history of previous episodes of pneumonia during the past 12 months was found to have no impact on the cure rate, but patients with pneumonia with bilateral involvement responded less well than those with single-lobe involvement. In the gatifloxacin group, the clinical cure rate was 86.7% (13/15) in patients with bilateral involvement versus 100.0% (4/4) for those with unilateral multilobe involvement and 100.0% (57/57) for those with single-lobe involvement. Corresponding cure rates in the ceftriaxone group were 92.3% (12/13), 83.3% (10/12), and 92.3% (48/52), respectively. (Statistical significance was not assessed.)

When all 170 treated patients were taken into account, the clinical cure rates in the 2 treatment groups (87.1% with gatifloxacin [74/85] vs 83.5% with ceftriaxone [71/85]) were statistically equivalent (95% CI, –9.9% to 16.9%; Table II). At the posttreatment follow-up assessment, no relapses occurred in either treatment group.

Table II. Clinical response and bacteriologic eradication rates among 170 patients randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD (n = 85) or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID (n = 85). Values are given as number (%) of patients.

Parameter	Gatifloxacin Group	Ceftriaxone Group
Clinical response		
Clinically evaluable patients*		
Cure	74/76 (97.4)	70/77 (90.9)
Failure	2/76 (2.6)	7/77 (9.1)
All treated patients†		
Cure	74/85 (87.1)	71/85 (83.5)
Failure	2/85 (2.4)	7/85 (8.2)
Unable to determine	9/85 (10.6)	7/85 (8.2)
Posttreatment follow-up		
Relapse	0/85 (0.0)	0/85 (0.0)
New infections‡	1/85 (1.2)	5/85 (5.9)
Bacteriologic eradication§ by pathogen		
All isolated pathogens	29/29 (100.0)	30/33 (90.9)
Haemophilus influenzae	12/12 (100.0)	12/12 (100.0)
Streptococcus pneumoniae	9/9 (100.0)	5/7 (71.4)
Staphylococcus aureus	5/5 (100.0)	5/6 (83.3)
Moraxella catarrhalis	1/1 (100.0)	4/4 (100.0)
Other bacteria‖	2/2 (100.0)	4/4 (100.0)

*95% CI for difference in cure rates: −3.7% to 19.1%.

†95% CI for difference in cure rates: −9.9% to 16.9%.

‡Gatifloxacin group: 1 urinary tract infection. Ceftriaxone group: 2 progressions of pneumonia; 2 sinusitis; and 1 each gingivitis and exacerbation of chronic bronchitis.

§Documented or presumed eradication; some patients had >1 pathogen isolated.

‖*Streptococcus pyogenes* (gatifloxacin, 1), *Acinetobacter baumannii* (gatifloxacin, 1; ceftriaxone, 2), *Enterobacter cloacae* (ceftriaxone, 1), *Providencia rettgeri* (ceftriaxone, 1), and *Acinetobacter calcoaceticus* (gatifloxacin, 1).

New infection occurred in 1 patient in the gatifloxacin group (a urinary tract infection) and 5 in the ceftriaxone group (2 instances of progression of pneumonia, 2 of sinusitis, and 1 each of gingivitis and an exacerbation of chronic bronchitis).

Bacteriologic Efficacy

Among 62 microbiologically evaluable patients (gatifloxacin, n = 29; ceftriaxone, n = 33), the eradication rate was 100.0% in the gatifloxacin group (29/29) and 90.9% in the ceftriaxone group (30/33; Table II; statistical significance was not assessed). In the ceftriaxone group, 3 pathogens persisted in 2 of 33 patients

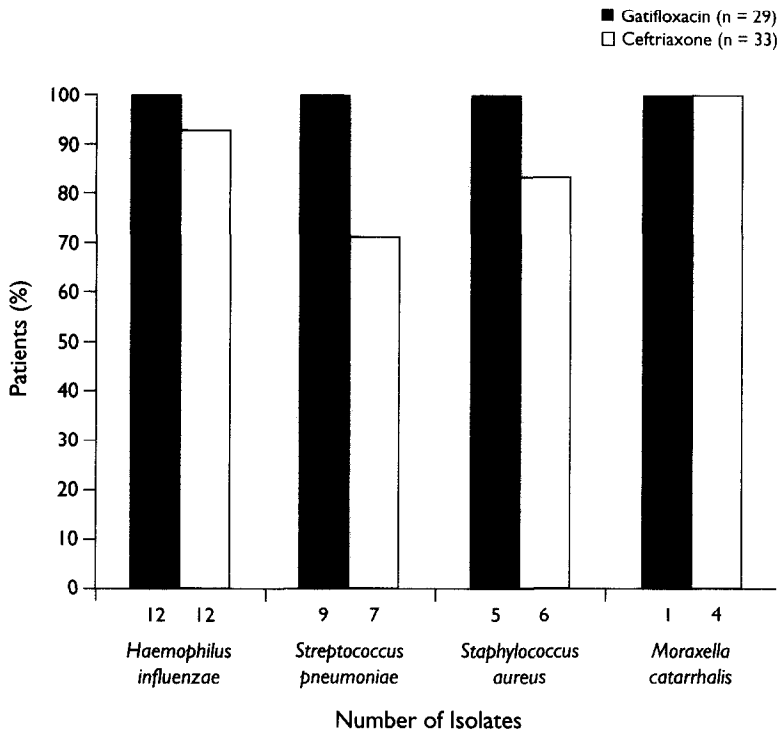

Figure 1. Clinical cure rates in microbiologically evaluable patients (clinically evaluable patients [those who had received ≥5 days of therapy, or 3 days in the cases of treatment failure] in whom a bacterial pathogen susceptible to the study drug was isolated from a pretreatment sputum culture) by pathogen. A total of 170 patients were randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID.

with pathogens at baseline (6.1%), both of whom were clinical failures. One had a penicillin-sensitive strain of *S pneumoniae* and the other a methicillin-sensitive strain of *S aureus* isolated from pretreatment sputum cultures.

Adverse Events

All 170 patients who were randomly assigned and received ≥1 dose of the study medications were included in the safety analysis. Five patients in each group discontinued the study because of adverse events. Twenty-three patients in

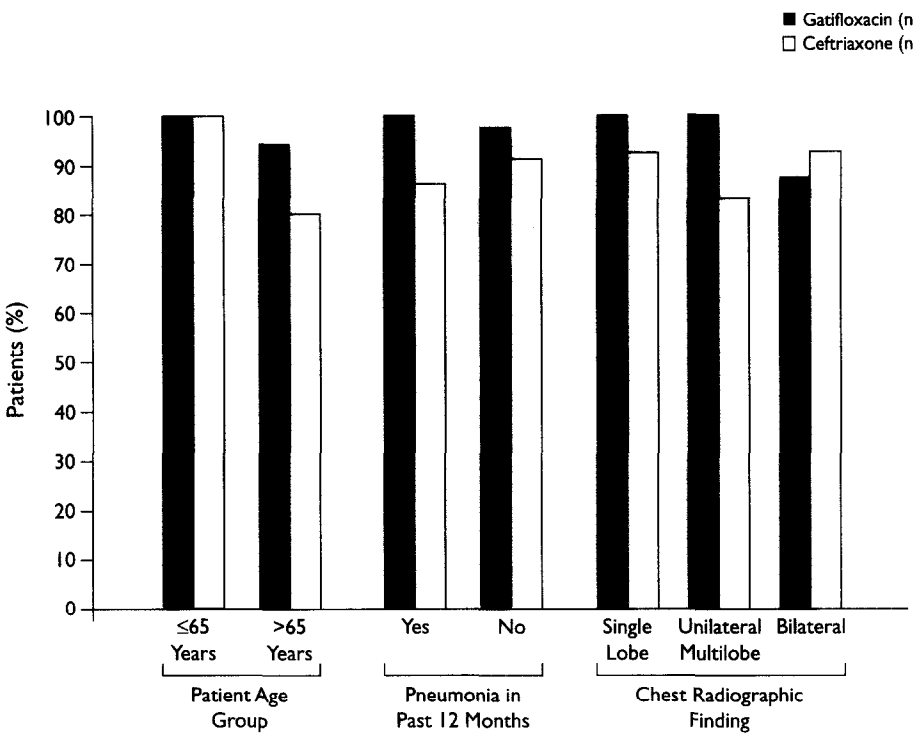

Figure 2. Clinical cure rates in 153 clinically evaluable patients (those who had received ≥5 days of therapy, or 3 days in the cases of treatment failure), grouped according to prognostic factor. A total of 170 patients were randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID.

the gatifloxacin group (27.1%) and 18 in the ceftriaxone group (21.2%) experienced treatment-related adverse events (Table III), most of which were mild or moderate in severity. Gastrointestinal symptoms were the most commonly reported adverse events, with nausea occurring in 7.1% of patients in the gatifloxacin group (6/85) and 4.7% of the ceftriaxone group (4/85). Two patients in each group (2.4% each) experienced serious treatment-related adverse events—pseudomembranous colitis and psychomotor agitation in 1 patient each with gatifloxacin (1.2% each), and urticaria and gastrointestinal hemorrhage in 1 patient each with ceftriaxone (1.2% each).

Table III. Adverse events considered related to the study medications and occurring in ≥2 patients in either treatment group among 170 patients randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD (n = 85) or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID (n = 85). Values are given as number (%) of patients.

Adverse Event	Gatifloxacin Group	Ceftriaxone Group
Nausea	6 (7.1)	4 (4.7)
Abdominal pain	3 (3.5)	1 (1.2)
Diarrhea	3 (3.5)	1 (1.2)
Phlebitis	3 (3.5)	2 (2.4)
Vomiting	3 (3.5)	2 (2.4)
Colitis	2 (2.4)	0 (0.0)
Dyspepsia	2 (2.4)	1 (1.2)
Pruritus/urticaria	2 (2.4)	3 (3.5)
Rash	2 (2.4)	0 (0.0)
Headache	0 (0.0)	2 (2.4)

A total of 154 abnormal laboratory values were noted during the study—129 in patients with normal pretreatment values (gatifloxacin, 65; ceftriaxone, 64); the other 25 involved worsened values in patients with abnormal pretreatment values (gatifloxacin, 15; ceftriaxone, 10). Among patients with normal pretreatment values (Table IV), the most frequently occurring laboratory abnormalities were decreased hemoglobin levels (gatifloxacin, 11; ceftriaxone, 14) and elevated alanine aminotransferase and aspartate aminotransferase activities (gatifloxacin, 28; ceftriaxone, 23). Hyperglycemic events in patients with normal baseline glucose values were reported in 17.6% (3/17) and 10.0% (1/10) of gatifloxacin- and ceftriaxone-treated patients, respectively, who had ≥1 value obtained during or after treatment. Among those with diabetes mellitus and abnormal fasting glucose levels at baseline, similar proportions of patients in the gatifloxacin and ceftriaxone groups (21.4% [3/14] and 22.2% [2/9], respectively) experienced a worsening of their fasting hyperglycemia. No reductions in fasting glucose values were reported among patients with normal baseline levels; 1 patient with diabetes mellitus and an abnormal baseline glucose level experienced a mild reduction in fasting glucose. Overall, most abnormalities were mild and did not require discontinuation of study medication.

DISCUSSION

The enhanced antibacterial activity of gatifloxacin relative to older fluoroquinolones (eg, ciprofloxacin, ofloxacin), particularly against *S pneumoniae* and *S aureus*,[11] and

Table IV. Laboratory adverse events (irrespective of relationship to treatment) in patients with normal pretreatment values among 170 patients randomized to receive 7 to 14 days of therapy with either IV gatifloxacin 400 mg QD with an option for stepdown to oral gatifloxacin 400 mg QD (n = 85) or IV ceftriaxone 1 or 2 g (with or without IV erythromycin lactobionate 0.5 or 1 g QID or IV clarithromycin 500 mg BID) with an option for stepdown to oral clarithromycin 500 mg BID (n = 85). Values are given as number (%) of events per group.

	Gatifloxacin Group		Ceftriaxone Group	
Laboratory Test	n*	No. (%) of Events	n*	No. (%) of Events
Alanine aminotransferase	55	15 (27.3)	58	9 (15.5)
Aspartate aminotransferase	48	13 (27.1)	57	14 (24.6)
Hemoglobin	42	11 (26.2)	52	14 (26.9)
Glucose increase	17	3 (17.6)	10	1 (10.0)
Blood urea nitrogen/urea	33	5 (15.2)	40	1 (2.5)
Creatinine	59	6 (10.2)	57	2 (3.5)
Neutrophils	68	4 (5.9)	64	9 (14.1)
Leukocyte count	74	4 (5.4)	71	4 (5.6)
Total bilirubin	88	2 (2.3)	22	3 (13.6)
Platelet count	58	1 (1.7)	61	3 (4.9)
Alkaline phosphatase	24	1 (4.2)	25	4 (16.0)
Any laboratory adverse event	566	65 (11.5)	517	64 (12.4)

*Number of patients with a normal pretreatment value who had ≥1 posttreatment value determined.

the favorable pharmacokinetic properties of gatifloxacin (long elimination half-life and high bioavailability),[12] which permit once-daily administration and IV-to-oral therapy switches, have led to its increasing use as empiric therapy for CAP. In this randomized, multicenter, multinational study of adults with CAP requiring hospitalization, 7 to 14 days of therapy with IV gatifloxacin 400 mg QD (with 91% of patients stepped down to oral gatifloxacin 400 mg QD after a median of 3 days) was as effective as a standard regimen of IV ceftriaxone 1 or 2 g QD with or without erythromycin 0.5 or 1 g QID or clarithromycin 500 mg BID (with 87% of patients stepped down to oral clarithromycin 500 mg BID after a median of 4 days). Among clinically evaluable patients, cure rates were 97.4% in the gatifloxacin group and 90.9% in the ceftriaxone group (95% CI for difference, −3.7% to 19.1%). The clinical response rate was also numerically higher with gatifloxacin in microbiologically evaluable patients (100.0% vs 87.9%; statistical significance not assessed). Patients in both groups who failed to respond to treatment were all aged >65 years. Cure rates in this older age group were 94.1% (32/34) and 80.0% (28/35) with gatifloxacin and the ceftriaxone regimen, respectively.

In this study, only a small number of patients had a confirmed bacterial pathogen at baseline. However, it is not unusual to find that only 30% to 50% of CAP patients have a documented bacterial etiology.[18] Collection of respiratory specimens can be difficult, and their interpretation is often complicated by insufficient numbers of organisms and contamination. Therefore, we only included bacterial isolates in our analysis if the collected respiratory secretions met predefined conditions (eg, >25 PMNs and <10 squamous epithelial cells per low–power field). The most commonly identified pathogens were *H influenzae, S pneumoniae, S aureus,* and *M catarrhalis,* all of which were sensitive to the study drugs. Similar to the clinical response rates, the bacteriologic efficacy of gatifloxacin was also numerically higher than that of the ceftriaxone regimen (statistical significance not assessed). In patients in whom pathogens were isolated from pretreatment sputum cultures, bacteriologic eradication rates were 100.0% in the gatifloxacin group and 90.9% in the ceftriaxone group.

Our results are consistent with those obtained by Fogarty et al[19] in a randomized, double-blind study at 45 North American sites involving 283 hospitalized patients with mild to severe CAP who received IV-to-oral stepdown regimens for 7 to 14 days (regimens almost identical to those used in the present study). The clinical cure rates reported by Fogarty et al[19] were 97% in patients who received gatifloxacin versus 91% in those who received ceftriaxone/clarithromycin with or without erythromycin (95% CI, –2.5% to 17.6). Thus, the efficacy of gatifloxacin for the treatment of hospitalized patients with CAP appears to be consistent in many parts of the world. In 2 other comparative studies against other classes of agents—1 in outpatients and 1 in hospitalized patients with CAP—oral or IV/oral gatifloxacin 400 mg QD produced clinical cure rates similar to oral clarithromycin 500 mg BID (95% vs 93%, respectively)[13] and IV/oral levofloxacin 500 mg QD (96% vs 94%, respectively).[14] Bacteriologic eradication rates in those 3 trials were similar but slightly higher with gatifloxacin (97% to 98%) versus the comparator regimens (92% to 93%). In the management of CAP, the antibacterial and pharmacokinetic properties of gatifloxacin, combined with its availability in both IV and oral formulations, may simplify the transition from IV to oral therapy in hospitalized patients. Treatment with gatifloxacin may allow faster conversion to oral therapy and, possibly, earlier discharge from the hospital. These suppositions warrant further study.

The gatifloxacin and ceftriaxone regimens were equally well tolerated in the present study. Treatment-related adverse events, most of which were mild or moderate in severity, occurred in 27.1% of patients in the gatifloxacin group and 21.2% of patients in the ceftriaxone group. The most commonly occurring adverse events with gatifloxacin were gastrointestinal symptoms, a finding that is similar to the results of other studies in a range of infectious diseases.[12] Available evidence suggests that gatifloxacin has a similar tolerability profile to ciprofloxa-

cin and does not cause either phototoxicity or neurotoxicity.[20] Although gatifloxacin appeared to have a higher rate of gastrointestinal adverse events than the ceftriaxone group in the present study, it is noteworthy that only 36.5% of the 85 patients in the control group (n = 31) received ceftriaxone plus a macrolide. Although the majority of ceftriaxone-treated patients who received concomitant macrolide therapy were given erythromycin, it is possible that the true rate of gastrointestinal adverse events was masked and is a low estimate of what would be observed in clinical practice.

CONCLUSIONS

In this randomized, open-label, parallel-group, multicenter study in adults with mild to moderate CAP requiring hospitalization, 7 to 14 days of treatment with IV gatifloxacin 400 mg QD with an option for oral stepdown gatifloxacin 400 mg QD was as effective for achieving clinical cure as a standard regimen of IV ceftriaxone 1 or 2 g QD (with or without IV erythromycin or clarithromycin) with an option for oral stepdown clarithromycin 500 mg BID. Both regimens were well tolerated.

ACKNOWLEDGMENTS

This study was supported by a grant from Bristol-Myers Squibb Company, Princeton, New Jersey. Editorial assistance was provided by Charles Miller, MA.

The principal investigators were as follows: *Argentina:* J. Altclas, MD, A.L. Dolmann, MD, and C. Luna, MD, Buenos Aires; J. Mera, MD, Mendoza; *Australia:* D. Langton, FRACP, Frankston; *Brazil:* R. Badaró, MD, Salvador; J.C. Corrêa, MD, and L. Mayrinck, MD, Rio de Janeiro; J. Mendonça, MD, and A. Tsanaclis, MD, São Paulo; *Mexico:* R. Diaz, MD, Guadalajara; G. Rico, MD, and M.A. Salazar, MD, Mexico City; M. Diaz, MD, M. Hernandez, MD, and L.G. Juarez, MD, Monterrey; J.A. Flores Villa, MD, Puebla; *Thailand:* Y. Supanitayanon, MD, and A. Vibhagool, MD, Bangkok; C. Bumroongkit, MD, Chiangmai; C. Chuchottaworn, MD, Nondhaburi.

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