Effectiveness, Safety and Tolerability of Gatifloxacin, a New 8-Methoxyfluoroquinolone, in the Treatment of Outpatients With Community-Acquired Pneumonia: A Brazilian Study

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Objectives: Evaluation of the effectiveness, safety and tolerability of gatifloxacin in the treatment of outpatients with community-acquired pneumonia (CAP). Study Design: A prospective, multicenter, non-comparative clinical study carried out in Brazil. Voluntary, unpaid physician participation contributed to an unbiased study design. Patients: Adult outpatients with clinical diagnosis of CAP. Regimen: Gatifloxacin, 400 mg PO once daily for 7 to 14 days. Study Procedures: Initial clinical assessment, at the first day of gatifloxacin therapy; final evaluation after 7 to 14 days of treatment. Results: According to the physicians' assessments 97.3% of patients were cured or improved after gatifloxacin treatment. The incidence of adverse events was low and the most commonly reported events were nausea and dyspepsia. Conclusions: Gatifloxacin, 400 mg PO once daily for 7 to 14 days, is effective and safe in the treatment of patients with CAP.
Key Words: Gatifloxacin, community-acquired pneunonia, Brazilian study.

Community-acquired pneumonia (CAP) is defined as a lower respiratory tract infection occurring in the community or within the first 48 hours after hospitalization. It remains one of the most common causes of infection-related morbidity-mortality, despite advances in diagnostic tests, antimicrobial therapy and specific vaccination.

During 1999, 969,752 patients diagnosed with pneumonia were admitted in hospitals pertaining to the "Sistema Único de Saúde – SUS" (Government Health Care System), in which 80% of population is attended. Considering the worldwide incidence of 12 CAP cases per 1,000 adult inhabitants, we can estimate an incidence of 1,920,000 cases per year. Based on this consideration more than 50% of affected Brazilians are being treated in hospitals, in contrast with the data received from other countries, where 80% of CAP are treated in ambulatory facilities [1].

According to SUS data, in Brazil, pneumonia is considered the first cause of death in respiratory diseases and, except for external causes, it is classified in fourth place in general mortality among adults [1]. These data reflect American statistics, classifying CAP as the sixth most important cause of general mortality [2,3].

In recent years, both the epidemiology and the treatment of CAP have changed, based on the recognition of new or previously non-identified pathogens, on the availability of more effective antibiotics and on the evolution of bacterial resistance mechanisms.

Organizations such as the American Thoracic Society (ATS) [2,3] and the Infectious Diseases Society of America (IDSA) [4,5] have proposed algorithms for empirical treatment of CAP. These are based on an assessment of the subjects (age, comorbidities), disease

Received on 22 March 2002; revised 16 July 2002.
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The Brazilian Journal of Infectious Diseases 2002;6(4):157-163

1413-8670

severity (related to the place indicated for the initial treatment: ambulatorial, hospital or intensive care unit) and pathogens known to be frequently associated with CAP in each specific condition. However, besides the careful assessment of these factors, the use of an antimicrobial agent requires knowledge about the activity of the antimicrobial agent against the presumed or known pathogen and its potential to induce bacterial resistance, besides safety and cost-effectiveness considerations [6].

Streptococcus pneumoniae, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila* remain the most common causative pathogens associated with CAP [7]. Though they are known to be relatively common organisms, increasing antimicrobial resistance of some of these pathogens to standard therapeutic regimens used in the treatment of PAC is a worldwide concern, due to the high prevalence rates of this disease.

S. pneumoniae remains the most important pathogen responsible for respiratory infections. Although resistance to penicillin does not represent a therapeutic problem in this condition (most resistant strains are susceptible to the therapeutic concentrations obtained in the plasma and pulmonary tissue), the choice of an antibiotic with low or no potential to induce resistance is critical in CAP treatment, to minimize the development of pneumococci highly resistant to penicillin [6,8,9].

Gatifloxacin is a new advanced generation 8-methoxifluoroquinolone that has an expanded spectrum of activity compared with previous generation quinolones [10,11]. It is active against gram-positive pathogens, including penicillin-resistant strains of *S. pneumoniae* and methicillin-susceptible *S. aureus*; gram-negative microorganisms, including *H. influenzae* and *M. catarrhalis*; atypical pathogens, such as *Mycoplasma*, *Legionella* and *Chlamydia* sp. [12-16]. When given by oral route, its bioavailability is 96% [17].

The efficacy of gatifloxacin in CAP treatment has been shown in randomized, double-blind (phase III) clinical trials, compared to levofloxacin [18], clarithromycin [19] and ceftriaxone ± erythromycin [20].

Further studies are needed to confirm the placement of a new drug after its approval, in order to evaluate its effectiveness and the incidence of serious adverse events when it is prescribed to large populations, in surveillance programs that do not follow protocol procedures required for randomized clinical trials [21].

This prospective, multicenter, non-comparative clinical trial, conducted in Brazil, assessed the effectiveness, safety and tolerability of gatifloxacin in the treatment of adult outpatients with CAP.

Materials and Methods

We made a large-scale, community-based assessment of the effectiveness, safety and tolerability of gatifloxacin for the treatment of patients with CAP examined by primary care physicians or community specialists. Five hundred and four physicians, across Brazil, participated in the study over a 6-month period from March to October, 2000. The participation of physicians in this study was entirely voluntary.

Study Population. Inclusion criteria: adult patients (> 18 years old) with clinical diagnosis of CAP, for whom oral therapy was indicated and who agreed to participate in this study.

Exclusion criteria: history of hypersensitivity reaction to fluoroquinolones; pregnancy or breast-feeding; inability to use an effective contraception method during the study; diagnosis of asthma or cystic fibrosis; nonbacterial respiratory tract infections; gastrointestinal disturbances affecting drug absorption.

Definition. CAP was diagnosed by pulmonary auscultatory findings, such as rales and/or egophony, associated with two or more of the following signs and symptoms: fever (> 38.0ºC), chest pain, cough, sputum production, chills or general discomfort [4].

Study Protocol. Each patient underwent a clinical examination on initiation of treatment and 7 to 14 days after therapy began. The evaluation of each patient was recorded in a case report form designed

for this study, completed by the responsible physician. The initial assessment included, besides the clinical diagnosis of CAP, based on the definition given above, demographics (age, sex), smoking history, history of previous respiratory tract infections (specimen and number within last 12 months before the study), exposure to antibiotics within 3 months before the study, and use of concomitant medications. At the time of the follow-up visit, patients were carefully questioned about any adverse events or reactions.

Patients were prescribed gatifloxacin 400 mg PO once daily for 7 to 14 days, at the discretion of the investigator. The drug could be administered without regard to meals.

Effectiveness assessment. Assessment of treatment effectiveness, defined as clinical response rate, was classified as:

(1) Cured: All symptoms of infection resolved and no additional antibiotic therapy was required;
(2) Improved: Evident reduction of infection symptoms, but incomplete resolution of some symptoms; no additional antibiotic therapy was required.
(3) Relapse: After initial improvement, the symptoms worsened during therapy, requiring maintenance of antibiotic therapy.
(4) Therapeutic failure: Poor improvement of the symptoms during antibiotic therapy.
(5) Unable to determine: Lost to follow-up, early termination of therapy or unable to assess due to interference by other conditions.

Adverse events assessment. Evaluation of adverse effects to the therapy was assessed throughout the medical report of the adverse event, including its intensity (mild, moderate, serious, extremely serious), relationship to the study drug (certain, probably, possibly, not likely), action taken regarding the study drug (none, dose reduction, interruption, discontinuation, dose increase) and the need for treatment.

Statistics. As the study was an open, non-comparative assessment of the effectiveness and the safety of gatifloxacin, only descriptive statistics were used for analysis of the results.

Results

Characteristics of the patients. A total of 1,501 patients were assessed, in different regions of the country, from March to October 2000. Demographic and clinical data are shown in Table 1.

Effectiveness. The physicians' evaluations of the responses to treatment showed that of the 1,501 patients, 1,460 (97.3%) were considered clinically cured (1,198) or improved (262) after receiving gatifloxacin therapy. Only 14 (0.9%) of the subjects were considered to have therapeutic failure (Table 2).

Safety and tolerability. Among the 1,501 assessed patients, 128 (8.5%) developed at least one adverse event.

Of a total of 158 adverse events, 109 were reported as probably, possibly or not likely related to gatifloxacin (Table 3).

One hundred and five adverse events (85.5%) were considered of mild or moderate intensity. Of the 20 adverse events considered as serious or extremely serious, those related to gatifloxacin therapy were gastrointestinal disturbances (nausea, vomiting, diarrhea, epigastric pain) and disturbances of the central nervous system (vertigo, chills, headache).

The most commonly reported adverse events in 128 patients were nausea (14%), dyspepsia (11%), diarrhea (7%), vertigo (6%) and headache (4%). All of these are typical adverse events seen in patients on antimicrobial therapy.

Discussion

Community-acquired pneumonia is one of the most common types of respiratory tract infections. In USA

Table 1. Demographics and clinical characteristics of 1,501 outpatients clinically diagnosed with CAP

Characteristic	
Age, years*	49 ± 19
Sex, Nº. (%)	
Male	718 (47.9)
Female	782 (52.1)
Not informed	1 (0.01)
Smoker, Nº. (%)	
Yes	330 (22.1)
No	1,166 (77.9)
Never smoked	688 (73.5)
Ex-smoker	248 (26.5)
Not informed	230 (19.7)
Not informed	5 (0.3)
Signs and Symptoms, Nº. (%)†	
Fever	1,324 (89.40)
Chest Pain	1,064 (71.84)
Cough	1,393 (94.06)
Sputum Production	1,172 (79.14)
Chills or malaise	1,181 (79.74)

* Mean ± SD.
† Referring to 1.481 patients: 20 (1.33%) patients without information.

Table 2. Effectiveness of gatifloxacin 400 mg PO once daily for treatment of 1,501 outpatients clinically diagnosed with CAP

Clinical evolution	Nº. (%)
Cured	1,198 (79.8)
Improved	262 (17.5)
Relapse	4 (0.3)
Failure	14 (0.9)
Unable to evaluate	23 (1.5)
Total	1,501 (100)

Table 3. Characteristics of 158 adverse events occurring in 128 outpatients clinically diagnosed with CAP

Intensity, N°. (%)	
Mild	75 (47.5)
Moderate	60 (38.0)
Serious	16 (10.1)
Extremely serious	4 (2.5)
Not informed	3 (1.9)
Relationship to the study drug, N°. (%)	
Certain	44 (27.8)
Probably	64 (40.5)
Possibly	38 (24.1)
Not likely	7 (4.4)
Not informed	5 (3.2)
Action taken related to the drug, N°. (%)	
None	126 (79.7)
Dose Reduction	2 (1.3)
Interruption	14 (8.9)
Discontinuation	9 (5.7)
Not informed	7 (4.4)
Treatment required, N°. (%)	
No	106 (67.1)
Yes	46 (29.1)
Not informed	6 (3.8)

it remains as the most common cause of infection-related mortality [2,3].

Community-acquired pneumonia (CAP) treatment is complex, due to a broad spectrum of potential etiological agents, the development of resistance among these pathogens and the difficulty to make a microbiological diagnosis, even with the use of sophisticated diagnostic tests. Due to these factors, antimicrobial therapy should be effective against common and atypical etiological agents and it is expected that new antibiotics will have high activity and minimal cross-resistance with other drugs [2,3,8,9].

Antimicrobial therapy should be started as early as possible for CAP treatment, for this reason, and due to the limitations of our current diagnostic methods, it is usually empirical. The options for antimicrobial therapy are in continuous development. For initial empirical therapy in immunocompetent adult patients, with no indication for hospitalization, to date advanced generation macrolides are recommended; doxycycline, β-lactam/macrolide combination and new fluoroquinolones (antipneumococcal fluoroquinolones) are other options [3,8,9].

The results observed in this study, with high cure or clinical improvement rates (97.3%) shown by patients with CAP who received gatifloxacin, were similar to the results of phase III studies [18-20] and another recent phase IV study, conducted in Mexico, of 3,322 patients with CAP treated with gatifloxacin, that had a success rate of 95.8% [22].

The adverse events observed with antimicrobial agents should also be considered and the choice of a safe agent for the treatment of CAP is required. The results of this study, which evaluated 1,501 patients with CAP, showed that adverse events related to gatifloxacin therapy were typical and similar to those observed with other antimicrobial therapies, such as nausea, diarrhea and headache.

Our study has some limitations. First, the definition of CAP that we used may be inadequate. We considered that possibility, but although we recommend that all patients with CAP should have a chest radiograph to establish the diagnosis and to determine if there are complications, in some outpatient settings this may be difficult or even impossible, depending on the time of the day and the availability of a radiology facility. Because this was a study of the effectiveness and safety of gatifloxacin in the "real world", outside the restricted environment of phase III clinical trials, we decided to use a clinical definition of CAP, which consisted of newly acquired respiratory or systemic symptoms or signals of infection accompanied by auscultatory findings of abnormal breath sounds and/or crackles. Although a diagnosis of pneumonia should be considered in any patient who has this clinical picture, these criteria do not have optimal sensitivity and specificity. Finally, we were unable to ascertain the number of patients that complied with the inclusion criteria during the study period but could not be fully evaluated. Actually, some of these (unevaluated) patients may have had different outcomes, but due to the sample size that we completely evaluated, we consider the results representative for the general population.

Based on our data and on a review of the literature [18-20,22], gatifloxacin is an important therapeutic option for CAP, due to its efficacy, effectiveness and the absence of known serious adverse events usually associated with other fluoroquinolones [23].

Conclusion

Oral gatifloxacin administered at a dosage of 400 mg PO once daily for 7 to 14 days was found to be effective and safe in this open, multicenter, non-comparative clinical trial of 1,501 outpatients clinically diagnosed with community-acquired pneumonia. Cure or clinical improvement occurred in 97.3% of the patients. The rate and seriousness of adverse events were low.

Acknowledgment:

The authors thank Bristol-Myers Squibb - Brazil for technical support during this study.

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