Gatifloxacin in the Treatment of Community-Acquired Pneumonias. A Comparative Trial of Ceftriaxone, With or Without Macrolides, in Hospitalized Adult Patients With Mild to Moderately Severe Pneumonia

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Community-acquired pneumonia is very common, but some of the cases do require hospitalization for treatment, particularly when older patients and/or co-morbidities are involved; both "typical" and "atypical" respiratory pathogens take part etiologically, and there is increasing concern about the emergence of resistance. There is interest in therapeutic options that can: a) comprehend such a spectrum of bacteria and resistance; b) allow parenteral to oral sequential treatment. We made a multicenter, prospective and randomized trial to compare the "standard" treatment of ceftriaxone IV alone or in combination with erythromycin IV, followed by clarithromycin PO (ceftriaxone treatment arm), with gatifloxacin IV, followed by oral administration (gatifloxacin treatment arm). The need for hospitalization was based on clinical criteria as judged by the investigators. Standardized criteria for diagnosis and follow-up were employed. Fifty-six patients were enrolled, with 48% over 65 years old, and there were frequent co-morbidities. Of these, 51 were clinically evaluable, 26 in the gatifloxacin and 25 in the ceftriaxone arm, with comparable success rates, 92% and 88%, respectively, even when major prognostic factors were considered. There were no serious adverse events or significant laboratory value changes attributable to the study drugs. Gatifloxacin as monotherapy (initially IV then orally until completion of treatment) was shown to be effective and safe, comparable to ceftriaxone IV alone or in combination with a macrolide (initially IV then orally until completion of treatment), in empirical therapy for community-acquired pneumonias, for patients that, at the physician's discretion, require initial treatment as inpatients.

Key Words: Ceftriaxone, gatifloxacin, pneumonias.

Community-acquired pneumonia (CAP) is a quite common clinical condition, and it is a major cause of morbidity and mortality among adults, mainly in elderly patients [1,2,4,6,9-12,19,21-23,25]. Since it is a disease that does not require mandatory communication, it's precise incidence is not well known, although there are some references of 12 cases per thousand inhabitants per year [19]. It is estimated that over three quarters of CAP patients are treated as outpatients [2,19], leaving inpatient treatment to a small fraction. A recent review of pertinent medical literature shows that this subject is being widely addressed, taking into account, among others, the following reasons [19]: a) a more accurate awareness of its etiology, mainly the role of the so-called "atypical " pathogens (*Mycoplasmapneumoniae, Chamydia sp.* a*nd Legionella sp.* [24,28,30] b) a more accurate severity assessment, with a better definition concerning the need for hospitalization [1,9-12,25,34]; c) definition of guidelines for antibiotic therapy, either empiric or specific [1,6,22,27]; d) evolution of antibiotic susceptibility in respiratory pathogens [16,18], especially resistance rates of *Streptococcus*

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pneumoniae [14,16,18,32]; e) the new antibiotics available, especially those used on respiratory pathogens, including the new quinolones [3,17,18,31] also called "respiratory" quinolones.

An important care decision certainly involves the need, or not, for hospitalization [2,9,21,23,25,26,34]. Fine et al. [10-12] have proposed predictive rules, considering the mortality risk at initial evaluation; however, they are not used on a routine basis and, therefore, the decision frequently remains at the physician's discretion, which is subject to individual variations. Furthermore, the shortest possible period of hospitalization is pursued, with the purpose of completing the treatment at home, with several advantages concerning the risks of hospital infections and costs.

Since pneumococci are the most commonly identified pathogens linked to CAPs [4,9,19,23], involved in at least one third of the cases, and knowing that they are evolving worldwide from susceptible to non-susceptible to beta-lactam antibiotics (related to penicillin) [16,18,32] and macrolides [5,14,16,18,20,32], the need for effective treatment alternatives is well recognized. In this context, the new quinolones are a worthy acquisition [3,17,18,31], partly since they also are potent against the so-called "atypical" pathogens, since clinical and radiological differentiation among the several etiological agents involved is not guaranteed [24,28,30].

Treatment of CAPs is typically an empirical, initially [4,6,9,19,21,22,25-27], since the delay in introducing antibiotic therapy, especially in patients requiring hospitalization, can be associated with an increased risk of complications and even death, mainly among elderly patients.

Gatifloxacin is a new fluorquinolone with a broad spectrum antibacterial activity, including the most common respiratory pathogens in the community [16,18,32]; thus, it is active against *S. pneumoniae* (including those strains not susceptible to penicillin), *Haemophilus influenzae, Moraxella catarrhalis*, several enterobacteriaceae, some anaerobic bacteria, *Mycoplasma sp.*, *Chlamydia sp.* and *Legionella sp.* Its pharmacokinetics [15,31] provides high respiratory concentrations and a long half-life, allowing once daily dosing, either intravenously (IV) or orally; moreover, pharmacodynamic evaluations show an effective action of gatifloxacin against pneumococci [3, 31]. Clinical studies with gatifloxacin in the treatment of CAPs have given good results, comparable that of other drugs (levofloxacin, clarithromycin, ceftriaxone with step-down therapy to clarithromycin)[13,29,33]; adverse events were generally reported as mild and self-limited.

Ceftriaxone, a third generation parenteral cephalosporin, is indicated in many guidelines and is widely recognized as the "standard" therapy for CAP patients requiring hospitalization [1,4,6,21,22,26]. However, as with other beta-lactam antibiotics, it is not active against "atypical" pathogens, and therefore the addition of a macrolide is recommended whenever there is a concern about the etiological participation of such agents [1,4,6, 22].

We evaluated the efficacy of gatifloxacin administered first intravenously (IV), and then orally through the end of treatment, compared to the standard therapy of ceftriaxone IV alone or in combination with a macrolide (beginning with erythromycin IV, followed by clarithromycin P.O.) for CAP patients requiring hospitalization. The bacteriological response rate, as well as safety of both treatment regimes, were also evaluated.

Material and Methods

An open, multicenter prospective trial was conducted at five centers in Brazil; patients were randomized by a central system ("Qtone™ system") into two groups of antibiotic therapy: a) gatifloxacin (400 mg once daily dose), starting by IV and then oral administration; b) ceftriaxone (1-2 g once daily dose) IV, with or without a macrolide (initially erythromycin 0.5-1 g/dose in four daily IV administrations, followed by clarithromycin 500 mg/dose twice daily (P.O.). Due to the possible etiological participation of "atypical" pathogens, the combination with a macrolide was left at the investigator's discretion. The treatment period, between 7 and 14 days for both groups, was a decision

of the investigator, as was the choice of ceftriaxone and erythromycin dosages. The minimal period of parenteral administration of antibiotics for both groups was determined as two days; after this period, it was left at the investigators' discretion when to switch to oral administration for patients receiving gatifloxacin and macrolide.

The study included male and female (documented non-pregnant) patients that were 18 years old or above, presenting clinical, laboratory and radiological data consistent with the diagnosis of community-acquired pneumonia. The diagnosis of pneumonia was based on findings of new infiltrate(s) in chest X-rays, and two or more of the following: fever (> 38° C); cough; chest pain; purulent sputum (> 25 neutrophils and < 10 squamous epithelial cells per field); pulmonary sounds, such as rales and egophony; leukocytosis (>10,000 leukocytes/mm^3 or > 15% of bands); presence of a predominant pathogen and neutrophils in a smear of material obtained by transtracheal aspirate, bronchial washing or biopsy; and identification of a predominant Gram-stained pathogen in material obtained by direct pulmonary aspirate or from blood cultures. The evaluation of pneumonia severity was based on *American Thoracic Society* [1] criteria, including cases of mild to moderate severity, which required hospitalization, according to the investigators.

Patients were excluded if they had: terminal diseases; documented or suspected tuberculosis, fungal or viral disease; neutropenia (< 1,000 leukocytes/mm^3); immune disease (including AIDS) or immunosuppressive therapy; renal failure; patients in bad conditions requiring mechanical ventilation at entry; empyema; hospital infection; hypersensitivity to any of the protocol antibiotics; gastrointestinal disorders impairing antibiotic absorption; use of systemic antibiotics within 14 days prior to the study; concomitant use of terfenadine, astemizole or cisapride (due to potential interaction with cytochrome P450).

Assessments were scheduled for the following time-points: pre-treatment; on-treatment (day 2 to day 4); end of treatment (up to three days after completion); post-treatment (one to two weeks after completion). At each time-point, the following procedures were performed: clinical evaluation (signs and symptoms); chest X-ray; laboratory tests (hematological, blood chemistry, urinalysis); blood cultures (serial, only if clinically indicated and/or previous positive blood culture) and respiratory samples for Gram staining and routine culture (serial, if clinically indicated), with susceptibility tests according to NCCLS standard; and adverse events evaluation. Clinical response was classified as: cure (resolution of acute pneumonia symptomatology, with antibiotic therapy being no longer necessary), failure (progression of acute pneumonia symptomatology after at least three days of treatment, with or without progression of radiological abnormalities), and undetermined (other circumstances preventing evaluation as cure or failure). Moreover, the occurrence of relapses (post-treatment revision) or a new infection, was also evaluated. Bacteriological response, considered only in cases of isolation of a pathogen during the pre-treatment period, was classified as: eradication (documented or presumed), persistence (documented or presumed) and undetermined. The occurrence of superinfections (isolation of a new pathogen) was also evaluated. Clinical and laboratory adverse events were evaluated (the latter by standardized grading from Grade I to IV) and judged by the investigators as related (possibly or probably) or unrelated to the antibiotics used in the study. Statistical analysis considered all treated patients, or clinically evaluable patients, using an exact method (Stat Xact-3®) for 95% confidence intervals. The ethical principles established in the Declaration of Helsinki and Good Clinical Practice were observed, Ethics Committees approval was obtained and informed consents were used.

Results

Between October 1999 and October 2000, 56 patients were enrolled, 29 and 27 in the gatifloxacin and ceftriaxone treatment arms, respectively. The mean patient age was 59.9 years (ranging from 23-91, 48% were over 65 years), 41% were male, with no significant difference between gatifloxacin and ceftriaxone groups.

In the ceftriaxone group, 30% were treated with 1g once daily dose; 11% had a macrolide added. Switching from IV to oral administration was possible in 77% of patients, i.e., in 23% of the cases, drug administration was IV only.

There were no differences between treatment groups regarding: pulmonary history (COPD and asthma being the most common, present in 10% of the cases); medical history (patients experiencing one or more medical conditions: cardiovascular disease, neurological disease and alcoholism were identified in 39%, 13%, and 5%, respectively); proportion of pulmonary involvement of acute pneumonia (one lobe: 61%; unilateral multiple: 14%; bilateral: 25%).

Among the 56 patients enrolled: 51 (91%) were classified as clinically evaluable, 26 in the gatifloxacin arm and 25 in the ceftriaxone treatment arm. The reasons why 5 patients became non-evaluable mostly included non-attendance for follow-up and inadequate dosing of the antibiotics. The results of clinical efficacy concerning 51 evaluable cases are shown in Tables 1 and 2; there were 5 failures, 2 in the gatifloxacin group and 3 in the ceftriaxone group. Overall, the cure rates were 92% and 88% for the gatifloxacin and ceftriaxone treatment arms, respectively, with no significant difference between the two arms, although the gatifloxacin arm had the highest cure rate. The analyses were similar, as a rule, when important prognostic factors were also considered (age > 65 years, previous history of pneumonia within the last 12 months, proportion of pulmonary involvement).

In 25 (45%) of the 56 initial patients, pathogens were isolated during the pre-treatment period, 15 in the gatifloxacin arm and 10 in the ceftriaxone arm. Multiple pathogens were identified in 6 patients, with 33 evaluable isolates discriminated (Table 3). Isolation from blood cultures was observed in one case, with retrieval of *Streptococcus pneumoniae*. Among the microbiologically valid cases, bacteriological eradication (documented or presumed) was found for 28 pathogens from the gatifloxacin arm (19 of 19), and from the ceftriaxone treatment arm (6 of 9) (Table 4). Clinical efficacy for the identified pathogens, involving clinically evaluable cases (Table 5), indicated success in all cases treated with gatifloxacin and 3 failures with ceftriaxone, one case each of *H. influenzae, S. pneumoniae* and *S.aureus*.

No relapses were observed in either group; new concurrent infections were observed in six patients, one in the gatifloxacin arm and five in the ceftriaxone arm. Overall, drug-related clinical adverse events were identified in 14 (48%) and 11 (41%) of the patients, respectively, in the gatifloxacin and ceftriaxone groups, with nausea, diarrhea and urticaria being the most common events (Table 6). No serious adverse event was related to the drugs used in this study. Grade III and IV laboratory abnormalities, occurring either after normal pre-treatment values or involving worsening of already altered results, occurred in one patient in the gatifloxacin arm (Table 7).

No deaths were reported through post-treatment evaluation (1-2 weeks after completion), and one death was reported within 30 days following the end of treatment, with no relation to the medications used in this study.

Discussion

CAP is a major cause of morbidity and mortality among adults,[1,2,4,6,9,10,19,22,23], especially those in older people. Around 80% of CAP patients are treated as outpatients, with a very low mortality rate [9,10-12,19, 23]; however, in more severe cases requiring hospitalization, this rate rises significantly [9,10-12,21], mainly in patients requiring treatment in the ICU and/or those placed on mechanical ventilation. The mean age of patients in this study group was 59.9 years, with 48% of them being over 65 years old; hospitalization was at the investigator's discretion, and the previous classification of cases according to severity varied from mild to moderate.

A variety of pathogens can be the cause of CAPs, with pneumococci accounting for the most frequently identified etiology, both in outpatients and in inpatients [4,9,19,23]. Other pathogens, including *Haemophilus influenzae, Staphylococcus aureus* and Gram-negative aerobic bacilli, are responsible for a smaller

Table 1. Clinical response among clinically evaluable patients

	Number of patients (%)		
Clinical Response	**Gatifloxacin**	**Ceftriaxone**	**Total**
Cure	24 (92)	22 (88)	46 (90)
Failure	2 (8)	3 (12)	5 (10)
Total	26	25	51

Table 2. Clinical cure rate by prognostic factor among clinically evaluable patients

	Cures/Evaluable patients (%)		
Prognostic Factor/Subcategory	**Gatifloxacin N = 26**	**Ceftriaxone N = 25**	**Total N = 51**
Patient age			
≤ 65 years	13/13 (100)	14/14 (100)	27/27 (100)
> 65 years	11/13 (85)	8/11 (73)	19/24 (79)
History of pneumonia during the last 12 months			
Yes	1/1 (100)	2/2 (100)	3/3 (100)
No	23/25 (92)	20/23 (87)	43/48 (90)
Chest X-ray reading			
Single lobe involvement	16/16 (100)	14/16 (87)	30/32 (94)
Unilateral multilobe involvement	2/2 (100)	5/5 (100)	7/7 (100)
Bilateral involvement	6/8 (75)	3/4 (75)	9/12 (75)

proportion of cases [2,4,6,9,19,21,23]. The so-called "atypical" pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella sp*) can affect a significant proportion of the patients [4], depending on the age group and geographical position. Some investigations have shown their etiological participation in about half of the cases [24,30]. In our investigation, *H. influenzae* and *S. pneumoniae* were the most common pathogens, found in around 60% of the isolates. All 9 isolated pneumococci were classified as susceptible. Since this sample is not representative, it is important to keep in mind that pneumococci resistance rates (MIC = > 2 μg/mL) can be high, though they differ by region, with a finding of 11.7% in Latin America [16]. This is a cause for concern, since resistance has been increasing over the years. There was no etiological evaluation aimed at "atypical" pathogens in this investigation; only one study conducted in Brazil has found that around half of the cases showed this etiology in CAP outpatients [30]. Taking into consideration "atypical" pathogens increases the interest in the choice of correct antibiotic

Table 3. Pre-treatment pathogens in all treated patients

Pathogen/Subtype	Gatifloxacin (%) N = 29	Ceftriaxone (%) N = 27	Total (%) N = 56
Number of patients with a pathogen	**15 (52)**	**10 (37)**	**25 (45)**
Single pathogen (%)	10 (67)	9 (90)	19 (76)
Multiple pathogens (%)	5 (33)	1 (10)	6 (24)
Number of Pathogens Isolated [a]	**22 (85)**	**11 (44)**	**33 (65)**
H. influenzae	7 (32)	4 (36)	11 (33)
β-lactamase $^{+}$	3 (43)	-	3 (27)
β-lactamase $^{-}$	4 (57)	2 (50)	6 (55)
β-lactamase unknown	-	2 (50)	2 (18)
S. pneumoniae	8 (36)	1 (4)	9 (18)
Penicillin-susceptible	8 (100)	1 (100)	9 (100)
Penicillin-resistant	-	-	-
Penicillin susceptibility unknown	-	-	-
S. aureus	5 (23)	2 (8)	7 (14)
Methicillin-susceptible	5 (100)	2 (100)	7 (100)
Methicillin-resistant	-	-	-
Other Gram-negative[b]	2 (9)	4 (36)	6 (12)

[a] A patient may have more than one pathogen isolated at pre-treatment.
[b] Gram-negative pathogens isolated included: *A.baumanii, A.calcoaceticus, P.aeruginosa.*

Table 4. Bacteriological eradication rate by pathogen, among microbiologically evaluable patients

Pathogens [a]	Number eradicated (documented or presumed)/ Number isolated (%)		
	Gatifloxacin N = 19	Ceftriaxone N = 9	Total N = 28
H. influenzae	7/7 (100)	3/3 (100)	10/10 (100)
β-lactamase $^{+}$	3/3	-	3/3
β-lactamase $^{-}$	4/4	1/1	5/5
β-lactamase unknown	-	2/2	2/2
S. pneumoniae	7/7 (100)	0/1 (0)	7/8 (88)
Penicillin-susceptible	7/7	0/1	7/8
Penicillin-resistant	-	-	-
Penicillin susceptibility unknown	-	-	-
S. aureus	3/3 (100)	1/2 (50)	4/5 (80)
Methicillin-susceptible	3/3	1/2	4/5
Methicillin-resistant	-	-	-
Other Gram-negative [b]	2/2 (100)	2/3 (67)	4/5 (80)
Total	**19/19 (100)**	**6/9 (67)**	**25/28 (89)**

[a] A patient may have more than one pathogen isolated at pre-treatment.
[b] Gram-negative pathogens isolated from 6 patients [as above]: *A. baumannii* (2/2), *A. calcoaceticus* (1/1), *P. aeruginosa* (1/2).

Table 5. Clinical cure rate by pathogen, among microbiologically evaluable patients

Pathogens [a]	Number eradicated (documented or presumed)/ Number isolated (%)		
	Gatifloxacin N = 19	**Ceftriaxone N = 9**	**Total N = 28**
H. influenzae	7/7 (100)	2/3 (67)	9/10 (90)
β-lactamase +	3/3	-	3/3
β-lactamase	4/4	1/1	5/5
β-lactamase unknown	-	1/2	1/2
S. pneumoniae	7/7 (100)	0/1 (0)	7/8 (88)
Penicillin-susceptible	7/7	0/1	7/8
Penicillin-resistant	-	-	-
Penicillin susceptibility unknown	-	-	-
S. aureus	3/3 (100)	1/2 (50)	4/5 (80)
Methicillin-susceptible	3/3	1/2	4/5
Methicillin-resistant	-	-	-
Other Gram-negative [b]	2/2 (100)	3/3 (100)	5/5 (100)
Total	**19/19 (100)**	**6/9 (67)**	**25/28 (89)**

[a] A patient may have more than one pathogen isolated at pre-treatment.

[b] Gram-negative pathogens isolated from 6 patients [as above]: *A. baumannii* (2/2), *A. calcoaceticus* (1/1), *P. aeruginosa* (2/2).

Table 6. Drug - related adverse clinical events among all treated patients

Clinical adverse events	Number of patients (%)	
	Gatifloxacin N = 29	**Ceftriaxone N = 27**
Asthenia	1 (3)	-
Anorexia	1 (3)	1 (4)
Diarrhea	3 (10)	1 (4)
Dyspepsia	1 (3)	-
Nausea	2 (7)	2 (7)
Abdominal pain	1 (3)	1 (4)
Vomiting	1 (3)	-
Dry mouth	1 (3)	-
Gastritis	-	1 (4)
Gastrointestinal hemorrhage	-	1 (4)
Headache	-	1 (4)
Hallucination	1 (3)	-
Bad Taste	1 (3)	-
Pruritus	1 (3)	-
Urticaria	-	2 (7)
Pain at injection site	-	1 (4)
Total	**14 (48)**	**11 (41)**

Table 7. Abnormal laboratory test values during or post-treatment in patients with normal pre-treatment values, including all treated patients.

	Number of patients (%)							
	Ceftriaxone (N = 27)				Gatifloxacin (N = 29)			
Laboratory test	**N[a]**	**Grade 1**	**Grade 2**	**Grade 3**	**N[a]**	**Grade 1**	**Grade 2**	**Grade 3**
Hemoglobin	6	6	-	-	2	2	-	-
WBC	3	2	1	-	2	2	-	-
Neutrophils	5	5	1	-	1	-	2	-
Platelets	-	-	-	-	-	-	-	-
Alkaline phosphatase	-	-	-	-	-	-	-	-
AST	5	5	-	-	5	5	-	-
ALT	4	4	-	-	6	6	1	1
Total Bilirubin	-	-	-	-	-	-	-	-
BUN/Urea	-	-	-	-	-	-	-	-
Creatinine	1	1	-	-	2	2	-	-
Glucose increase	-	-	-	-	1	1	-	-
Total occurerences	24	23 (96)	2 (8)	-	19	18 (95)	3 (16)	1 (5)

[a] For each test, number of patients with a normal pre-treatment value who had at least one abnormality in their blood data during or post-treatment.

therapy (no activity of penicillin/beta-lactams), especially for patients whose case severity demands hospitalization; although in an empirical manipulation, 11% of the cases in the ceftriaxone treatment arm required the addition of a macrolide. Gatifloxacin gives an expectedly useful therapeutic action, based on the performance identified *in vitro* [3,17,18].

Even in investigations using diagnostic procedures that are not routinely performed, including those tailored to the identification of "atypical" pathogens, an important percentage of CAP cases remains without etiological identification [9,19]. Moreover, from a clinical and radiological point of view, it is not possible to make a guaranteed etiological differentiation of a specific agent, including the distinction between "typical" and "atypical" pathogens [24,28,30]. Consequently, the treatment of CAPs is characteristically an empirical procedure during the initial care of the patient [4,6,9,19,21,22,25-27], and it must be taken into consideration that the delay in beginning antibiotic therapy may be associated with an increased risk of complications, and even death [25,26]. This consideration is particularly important when hospitalized patients are involved, since they generally have a more serious disease condition, are older and have concomitant morbid conditions. A significant number of patients with previous pulmonary conditions (COPD and asthma) and other disorders (cardiovascular disease, neurological disease, and alcoholism) were identified in our sample.

The variable condition of CAPs patients requiring hospitalization impels us to make an appropriate initial choice of antibiotic therapy. Several guidelines have been published [1,6,22,27] and periodically updated, and although they do not necessarily agree with each other, they intend to indicate criteria for antibiotic therapy that are appropriate for CAPs. In situations corresponding to those of our study, for example, the following alternatives are offered: for patients requiring admission to hospital and being treated in a medical ward, both IDSA [6] and CIDS [22] guidelines recommend a fluorquinolone for monotherapy or a beta-lactam plus a macrolide. A recent Brazilian Consensus [27] indicates a respiratory quinolone alone,

or the systematic combination of a macrolide with an injectable second, third or fourth generation cephalosporin. Considering that pneumococci can be resistant to macrolides, macrolide monotherapy may result in therapeutic failure [20].

As long as ciprofloxacin was available, fluorquinolones did not gain major acceptance as an appropriate monotherapy for CAPs, because in spite of having excellent activity against Gram-negative pathogens, they have lesser activity against Gram-positive pathogens, particularly pneumococci [8]. The new fluorquinolone generation keeps most of the activity against Gram-negative and also gives much better activity against Gram-positive pathogens, including pneumococci, both susceptible and non-susceptible to penicillin [3,16-18]. Moreover, they also act favorably against the so-called "atypical" pathogens, have favorable pharmacokinetics in the respiratory system and are relatively well tolerated.

Gatifloxacin is a new fluorquinolone that shows broad spectrum activity against community respiratory pathogens [16-18]; consequently, it is active against pneumococci (including strains unsusceptible to penicillin), *H. influenzae*, *M. catarrhalis*, many enterobacteriaceae and anaerobic bacteria, *Mycoplasma*, *Chlamydia* and *Legionella*. From a pharmacokinetic viewpoint [15], gatifloxacin has a long half-life, thus allowing once-a-day administration; pharmacodynamic assessments favor an effective action of gatifloxacin against pneumococci [3,31].

Clinical investigations made with CAPs outpatients, testing gatifloxacin in comparison with several alternative drugs (clarithromycin, levofloxacin) [29,33], have shown an overall clinical efficacy of 96% for gatifloxacin *vs*.93% to 94% for the other drugs. Bacteriological eradication was 98% for gatifloxacin *vs*. 93% for comparators. In an investigation conducted in Mexico [7], on outpatients with community respiratory infections, clinical efficacy in CAP cases was 95.8%. The most frequently reported adverse events were: nausea (2.76%), headache (2.2%) and dizziness (1.33%); and these were generally mild and self-limiting.

On the other hand, ceftriaxone, a third generation cephalosporin, is correctly pointed out by many authors as the "standard" therapy for patients with CAP who require hospitalization [1,4,6,21,22,26]; however, like other beta-lactam antibiotics, it has no activity against "atypical" pathogens, thus the addition of a macrolide is recommended whenever there is concern about etiological participation of these agents [1,4,6,22]. An investigation comparing gatifloxacin *vs.* ceftriaxone, with step-down therapy to clarithromycin, showed a clinical efficacy of 96% *vs*. 91% and microbiological eradication of 98% *vs.* 92%, respectively [13].

In our study, we compared the efficacy and safety of gatifloxacin (daily, initially IV, and then switching to oral administration), with that of ceftriaxone (daily dosing, with or without the addition of erythromycin IV, switching to clarithromycin P.O.) in patients with CAP, who at the investigator's discretion, required hospitalization. A total of 56 patients were enrolled, 51 of them evaluable for clinical response. Cure rates achieved were very favorable, although with higher values in the gatifloxacin treatment arm when compared to ceftriaxone arm (92% *vs.* 88%, respectively), with no significant difference between the two. Cure rates including all 56 patients enrolled (intent to treat analysis) were 83% and 81%, respectively; however, 5 of them were excluded from the final clinical evaluation. Considering patients valid from a microbiological viewpoint, the pathogen eradication rates (documented or presumed) favored the gatifloxacin treatment arm (100% *vs.* 67% for clinical valid cases). At the clinical comparison level, 95% confidence intervals showed equivalence between gatifloxacin and ceftriaxone, with or without macrolide.

Considering the safety profile: drug-related clinical adverse events were mostly mild to moderate in severity, and were mostly related to the gastrointestinal system, with nausea and diarrhea as the most common events reported. Reaction at sites of antibiotics IV administration occurred only in the ceftriaxone treatment group (21%).

Based on ourinvestigation we conclude that gatifloxacin is equivalent to ceftriaxone, with or without macrolide, for the treatment of mild to moderate CAPs that require hospitalization. Gatifloxacin, however, offers

the following additional benefits: simpler dosing, reliable activity against strains of pneumococcus unsusceptible to penicillin, and a favorable safety profile. Moreover, it is feasible to switch from IV to oral administration [34] using the same medication in the antibiotic therapy of these patients with CAPs, which after achieving a clinical stable condition on a short-term parenteral therapy, may be able to continue their treatment at home.

Conclusions

Gatifloxacin as monotherapy (initially IV and, when feasible, orally until completion of treatment) was found to be effective and safe, comparable to ceftriaxone IV alone or in combination with a macrolide (initially IV and, when feasible, orally until completion of treatment), in empirical therapy of community-acquired pneumonias, involving adult inpatients with mild to moderate pneumonia. Due to its activity against ordinary respiratory pathogens (including pneumococci unsusceptible to penicillin) and also against the so-called "atypical" pathogens, gatifloxacin is a valuable therapeutic option for the treatment of these patients, allowing the maintenance of the same medication for antibiotic therapy after early discharge from the hospital.

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