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A randomised, double-blind, double-dummy comparative study of gatifloxacin with clarithromycin in the treatment of community-acquired pneumonia

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ABSTRACT

Eligible patients were randomised in this multicentre, randomised, double-blind, double-dummy parallel-group study in a ratio of 1:1 to either gatifloxacin 400 mg once-daily for 5–14 days plus matching placebo, or clarithromycin 500 mg twice-daily for 5–14 days. The primary outcome measure was clinical response (clinical cure plus improvement) at the end of treatment. Secondary endpoints were clinical response at end of study, clinical cure at end of treatment and end of study, bacteriological response at end of treatment and end of study, and treatment duration. The overall clinical response was similar in the two treatment groups, with 92.2% of gatifloxacin-treated patients cured or improved at the end of treatment, compared with 93.1% of those receiving clarithromycin. Corresponding bacteriological response rates (eradication plus presumed eradication) were 96.7% and 87.5%, respectively. The study drugs were well-tolerated, with nausea (gatifloxacin) and bitter taste (clarithromycin) being the only treatment-related adverse events with a frequency of > 5%. No patients experienced phototoxicity, hepatic or renal dysfunction, tendonitis or crystalluria. Oral gatifloxacin 400 mg once-daily appeared to be a safe and effective alternative to clarithromycin in the treatment of community-acquired pneumonia.

Keywords Clarithromycin, community-acquired pneumonia, gatifloxacin

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INTRODUCTION

The changing aetiology of community-acquired pneumonia, reflected by the increasing isolation of atypical respiratory pathogens, and a rising prevalence of resistance to standard antibiotics among common respiratory pathogens, necessitates consideration of new treatment strategies [1,2]. While various European professional bodies and authorities still recommend oral penicillins and cephalosporins as first-line agents for community-acquired pneumonia [3,4], treatment outcome can be compromised severely by the presence of penicillin-resistant *Streptococcus pneumoniae* and β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. Furthermore, atypical respiratory pathogens, such as *Legionella pneumophila*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, are not susceptible to β-lactam antibiotics. Increasingly, modern macrolides, such as clarithromycin and azithromycin, are recommended for empirical treatment of community-acquired pneumonia because of additional activity against atypical respiratory pathogens [5]. However, with the increasing resistance of respiratory pathogens against macrolides, especially in southern European countries, the newer broad-spectrum fluoroquinolones represent a potential alternative as first-line agents for community-acquired pneumonia. These compounds possess activity against both Gram-positive and

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Gram-negative respiratory pathogens, including multiresistant strains, and are highly active against atypical respiratory pathogens [6].

Gatifloxacin is a new advanced-generation 8-methoxy fluoroquinolone. It combines broad-spectrum antibacterial activity against all the typical and atypical respiratory pathogens, including penicillin- and macrolide-resistant *S. pneumoniae* [7–10], with a pharmacokinetic profile that includes good absorption following oral dosing, excellent penetration into the respiratory tract, and a long plasma half-life enabling once-daily dosing [11]. Importantly, it shows no evidence of serious fluoroquinolone-related side effects, such as phototoxicity or central nervous system toxicity, and its high metabolic stability confers a low interaction potential. With regard to adverse cardiac effects (QT-interval prolongation), another typical feature of the fluoroquinolone class, gatifloxacin is comparable to moxifloxacin [12].

In this multinational, multicentre phase III study, the efficacy, safety and clinical and bacteriological properties of oral gatifloxacin 400 mg once-daily were compared with those of oral clarithromycin 500 mg twice-daily in 286 adult patients with community-acquired pneumonia.

METHODS AND MATERIALS

Patients

Adult male and female patients (aged ≥18 years) with community-acquired pneumonia of mild-to-moderate intensity were eligible for enrolment. Evidence was required of new infiltrates on chest X-ray within 48 h of initiation of therapy, and signs and symptoms of typical pneumonia (cough, rales, pulmonary consolidation, chest pain) or atypical pneumonia (myalgia, headache, moderate fever without chills, dry cough with little expectoration). In addition, evidence of either fever (> 38°C) within the past 24 h or a blood white cell count of >10 000/mm^3 was required. Written informed consent was given before enrolment to the study.

Major exclusion criteria included pregnancy, lactation, nosocomial pneumonia, severe concomitant disease, allergy, severe dehydration, blood donation (> 500 mL) within the previous 3 months, the need for antibiotic therapy for other infectious diseases, or immunosuppressive therapy. A history of psychiatric illness or suicide risk within the previous 2 years, evidence of alcohol, substance or drug abuse, or any condition likely to affect the disposition of study medications, were also criteria for exclusion.

Study design

This randomised, double-blind, double-dummy parallel-group study compared the efficacy and safety of oral gatifloxacin with that of oral clarithromycin in patients with community-acquired bacterial pneumonia. The protocol complied with the Guidelines for the Clinical Evaluation of Anti-infective Products [13], was approved by the appropriate ethics committees in each country, and was carried out in accordance with the Declaration of Helsinki. Eligible patients were randomised in a ratio of 1:1 to either gatifloxacin 400 mg once-daily for 5–14 days plus matching placebo, or clarithromycin 500 mg twice-daily for 5–14 days.

Pre- and post-treatment assessments

Patients gave a detailed medical history and underwent a complete physical examination for clinical signs and symptoms of pneumonia, together with an assessment of vital signs, a chest X-ray and laboratory investigations. Repeat physical examinations, together with assessments of vital signs, as well as clinical signs and symptoms of pneumonia, were carried out during treatment (days 4–6), at end of treatment (days 1–3 post-treatment), and at end of study after 2–4 weeks. Chest X-rays were performed again at end of treatment and, if clinically necessary or not performed at end of treatment, at end of study.

For microbiological assessment, sputum specimens were obtained for Gram's stain, culture and susceptibility testing within 48 h of drug administration, and were, if possible, repeated at each subsequent study visit. Specimens were obtained from expectorated sputum (including saline nebulisation), or by trans-tracheal aspiration, endotracheal aspiration, trans-thoracic fine needle puncture and bronchoscopic procedures, such as bronchoalveolar lavage, bronchoscopic-protected catheter brush, pleural fluid or lung biopsy. Venous blood samples were collected for culture and serology. Serological diagnosis of atypical pneumonia, caused by pathogens such as *C. pneumoniae*, *Coxiella burnettii*, *M. pneumoniae* and *L. pneumophila*, was based on a four-fold increase in the antibody titre of paired sera. Immunofluorescence tests were performed on bronchoalveolar lavage specimens for diagnosis of *L. pneumophila*.

The primary outcome measure was clinical response (clinical cure plus improvement) at the end of treatment, in which cure was defined as a complete resolution of all signs and symptoms of pneumonia, together with improvement or lack of progression of imaging, and no reason for clinical failure. Clinical improvement was defined as resolution of >50% of all signs and symptoms of pneumonia, together with improvement or lack of progression of imaging, resolution of fever if elevated at enrolment, and no reason for clinical failure. Clinical failure was defined as persistence or progression of pneumonia after therapy for 3–5 days, lack of improvement in clinical signs and X-ray at end of treatment, or lack of resolution of >50% of signs and symptoms of pneumonia. Further reasons for clinical failure included additional, or change of, antibiotics because of pneumonia, new pulmonary or extra-pulmonary clinical findings consistent with active infection, presence of fever, progression of pneumonia related to radiographical abnormalities, withdrawal because of drug-related adverse events, or death caused by pneumonia.

Bacteriological outcome was considered to be successful if eradication or presumed eradication of the causative organism was achieved at end of treatment or end of study, with or without colonisation. Eradication was defined as elimination of the original causative organism(s) from the same site, and presumed eradication was defined as the absence of culture

material because the patient had improved clinically and did not produce sputum, or because repeated aspiration of pleural fluid was not justified on clinical grounds. Colonisation was defined as the development of a positive sputum culture, with a bacterial strain other than the primary causative organism appearing > 48 h after initiation of therapy and persisting in at least two repeated cultures in the absence of fever, leukocytosis, persistence or progression of pneumonia, or evidence of infection at a distant site. Bacteriological response was considered to be unsatisfactory if there was a failure to achieve eradication or presumed eradication, or if the patient relapsed, became reinfected, or acquired a superinfection with a new or resistant pathogen not identified as the original causative organism.

Safety analyses were based on the incidence and severity of all adverse events and their relationship to study medication, as well as changes from baseline in vital signs and laboratory parameters. All patients who received at least one dose of study medication were included in the safety analyses.

Statistical analysis

Sample size estimation, based on the assumption of an 80% clinical response for both treatments, a maximum acceptable difference of 15% and a dropout rate of 15%, required 136 patients in each treatment arm. Efficacy analyses were based primarily on the modified intent-to-treat population, which included all patients who had received at least one dose of study medication and had the study disease. To compare efficacy between gatifloxacin and clarithromycin, a two-sided 95% confidence interval (CI) for the difference in clinical response was calculated according to Farrington and Manning [14]. No inferiority was demonstrated if the lower bound of the two-sided 95% CIs for the observed difference did not exceed −15%. Clinical cure rates in each group were summarised with 95% CIs calculated according to Hollander and Woolfe [15]. All analyses were one-sided. The same statistical procedures were used for analysis of secondary endpoints, which included clinical response at the end of study, clinical cure rates and bacteriological response rates. All other secondary endpoints were compared using descriptive statistics.

RESULTS

Patients

In total, 286 patients were randomised to treatment, of whom 141 (49.3%) received gatifloxacin 400 mg and 145 (50.7%) clarithromycin 500 mg. The two treatment groups were comparable with respect to patient disposition, demographic characteristics and causative pathogens isolated at admission (Tables 1 and 2).

Clinical and bacteriological outcome

Of the 286 patients randomised to treatment, all received at least one dose of study drug and were included in the modified intent-to-treat efficacy and safety analyses. Based on an optional treatment duration of 5–14 days, as stipulated in the study protocol, 37% of gatifloxacin-treated patients vs. 47% treated with clarithromycin received treatment for 7–10 days, while 55% vs. 49%, respectively, received treatment for 10–14 days. Overall, duration of therapy was similar in both treatment groups, with gatifloxacin administered for an average of 10.8 days and clarithromycin for 10.7 days.

Overall clinical response was similar in the two treatment groups, with 92.2% of gatifloxacin-treated patients cured or improved at the end of treatment, compared with 93.1% of those receiving clarithromycin. Corresponding rates at end of study were 93.4% and 94.2%, respectively. The two-sided 95% CIs for the difference between treatments at both end of treatment (– 7.62%; 5.90%) and end of study (– 7.33%; 5.78%) were well within the specified limit, indicating clinical equivalence. Although the two antibiotics exhibited equivalent efficacy, gatifloxacin achieved higher rates of clinical cure than clarithromycin at both end of treatment (68.1% vs. 59.7%,

Table 1. Summary of patient demographics and smoking history

Characteristics	Gatifloxacin 400 mg once-daily (n = 141)	Clarithromycin 500 mg twice-daily (n = 145)
Male	80 (56.7%)	79 (54.5%)
Female	61 (43.3%)	66 (45.5%)
Mean age, years (SD)	48.9 (16.71)	50.0 (18.48)
Age range, years	16–86	18–89
Mean weight, kg (SD)	74.1 (14.48)	72.4 (13.34)
Weight range, kg	37–32	46–125
Smoking history		
Never smoked	61 (43.3%)	68 (46.9%)
Current smoker	54 (38.3%)	50 (34.5%)
Ex-smoker	26 (18.4%)	27 (18.6%)

Table 2. Causative pathogens isolated most frequently at admission

	Gatifloxacin (n = 141)	Clarithromycin (n = 145)
Number of typical pathogens	32 (100%)	47 (100%)
Gram-positive organisms		
Streptococcus pneumoniae	11 (34.4%)	11 (23.4%)
Penicillin-susceptible	10 (31.2%)	10 (21.3%)
Penicillin-intermediate	1 (3.1%)	1 (2.1%)
Other streptococci	2 (6.3%)	10 (21.2%)
Staphylococcus aureus	0	2 (4.3%)
Gram-negative organisms		
Haemophilus influenzae	15 (46.9%)	19 (40.4%)
Moraxella catarrhalis	2 (6.3%)	1 (2.1%)
Haemophilus parainfluenzae	0	2 (4.3%)
Enterobacteriaceae	2 (6.3%)	2 (4.3%)
Number of atypical pathogens	22 (100%)	18 (100%)
Mycoplasma pneumoniae	17 (49%)	15 (47%)
Chlamydia pneumoniae	3 (8%)	3 (9%)
Coxiella burnetti	2 (5%)	0

respectively) and end of study (81.8% vs. 76.1%, respectively). However, these differences did not reach statistical significance. Only ten patients in each group failed to respond to treatment; this was associated mostly with the need for a new or additional antibiotic. Failure because of drug-related adverse events affected one patient in each treatment group.

Broad-spectrum antimicrobial activity was exhibited by both drugs, as shown by the clinical responses for the most common typical and atypical pathogens isolated at baseline (Table 3). Clinical success was accompanied by a marked improvement in clinical symptoms, and evidence of resolution of infection on chest X-ray in both treatment groups. Improvement was greatest in the gatifloxacin-treated group with respect to resolution of expectoration (88.6% vs. 80.6%, respectively), dyspnoea (76.4% vs. 72.9%, respectively), and improvement on chest X-ray (97.8% vs. 89.7%, respectively), but the difference was not statistically significant.

Within the modified intent-to-treat population, 32 (23%) of the gatifloxacin-treated patients and 47 (32%) of the clarithromycin-treated patients had typical bacterial pathogens isolated at baseline, of which *H. influenzae* and *S. pneumoniae* were by far the most common. Consistent with the clinical results, no significant difference was observed in bacteriological efficacy between the two treatments, with 96.7% of gatifloxacin-treated patients responding to treatment, compared with 87.5% of those treated with clarithromycin. Gatifloxacin successfully eradicated all strains of *S. pneumoniae* and 93.3% of *H. influenzae* strains at end of treatment, compared with rates of 90% and 88.9%, respectively, with clarithromycin.

Table 3. Response in clinically evaluable patients in relation to baseline pathogen following treatment with gatifloxacin or clarithromycin

Clinically evaluable patients with pathogens	Clinical response to gatifloxacin	Clinical response to clarithromycin
Typical pathogens		
Haemophilus influenzae	14/15 (93.3%)	18/19 (94.7%)
Streptococcus pneumoniae	10/11 (90.9%)	9/11 (81.8%)
Streptococcus pyogenes	1/1 (100%)	3/3 (100%)
Viridans streptococci		4/4 (100%)
Moraxella catarrhalis	2/2 (100%)	1/1 (100%)
Atypical pathogens		
Mycoplasma pneumoniae	13/13 (100%)	13/13 (100%)
Chlamydia pneumoniae	2/2 (100%)	2/2 (100%)
Coxiella burnetti	2/2 (100%)	

Table 4. Summary of the most frequent (≥ 1% patients in either group) treatment-related adverse events following administration of gatifloxacin or clarithromycin

Adverse event	Gatifloxacin (n = 141)	Clarithromycin (n = 145)
Nausea	8 (5.7%)	2 (1.4%)
Bitter taste	0	10 (6.9%)
Diarrhoea	6 (4.3%)	3 (2.1%)
Headache	0	4 (2.8%)
Increased hepatic enzymes	3 (2.1%)	1 (< 1.0%)
Increased SGPT	0	4 (2.8%)
Vomiting	2 (1.4%)	2 (1.4%)
Loose stools	0	3 (2.1%)
Metallic taste	2 (1.4%)	1 (< 1.0%)
Dizziness	2 (1.4%)	0
Heartburn	0	2 (1.4%)
Dry mouth	0	2 (1.4%)

SGPT, serum glutamic pyruvic transaminase (alanine aminotransferase).

Three patients yielded positive blood cultures for *S. pneumoniae* (two in the gatifloxacin group and one in the clarithromycin group) at admission. No further cultures were obtained during or after treatment, but according to the results of clinical outcome, all three patients were considered to have responded both clinically and bacteriologically.

Safety

Both study drugs were well-tolerated, with nausea (gatifloxacin) and bitter taste (clarithromycin) being the only treatment-related adverse events at a frequency of >5% (Table 4). Adverse reactions indicative of phototoxicity, hepatic or renal dysfunction, tendonitis, or temafloxacin syndrome, were not observed in any patient, and there were no cases of crystalluria. Nine patients experienced serious adverse events, which resulted in eight (2.8%) patients discontinuing treatment. Apart from one patient who experienced nausea, vomiting and tachycardia while receiving gatifloxacin, all other serious adverse events were considered to be unrelated to the study drugs. Overall, no clinically meaningful changes from baseline were observed in relation to clinical chemistry, haematology and urinalysis parameters. Changes in vital signs were consistent with improvement in disease status.

DISCUSSION

Community-acquired pneumonia is among the most common infections of the lower respiratory tract, and is a major cause of morbidity and

mortality in elderly patients. While early administration of antibiotic therapy can reduce significantly the high rates of morbidity and mortality associated with community-acquired pneumonia [16], the choice of first-line agents for empirical use is today complicated by the rising prevalence of resistance to standard antimicrobial agents. In some countries, almost 50% of *S. pneumoniae* isolates show reduced susceptibility to penicillin, while cross-resistance among penicillin-resistant isolates to other agents, such as cephalosporins and macrolides, is common [17,18]. While *H. influenzae* was once universally susceptible to ampicillin, recent data from the Alexander Project show that the prevalence of β-lactamase-producing strains of *H. influenzae* now exceeds 20% in parts of Europe [17]. Almost all strains of *M. catarrhalis* produce β-lactamases and also exhibit resistance to trimethoprim [19]. At the present time, effective empirical antimicrobial therapy for community-acquired pneumonia requires antibiotics that cover not only the typical respiratory pathogens, but also the atypical intracellular pathogens that are being isolated with increasing frequency from cases of community-acquired pneumonia [20].

The results of the present study show that oral gatifloxacin 400 mg once-daily is a safe and highly effective alternative to twice-daily clarithromycin in the treatment of community-acquired pneumonia. These results are supported by other studies in which gatifloxacin has been used to treat patients with community-acquired pneumonia, including those infected with multiresistant strains of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, as well as atypical pathogens [21–24].

The choice of empirical therapy for community-acquired pneumonia is also governed by an antibiotic's safety and tolerability profile. The present study showed that the high rates of clinical and bacteriological efficacy achieved with gatifloxacin were accompanied by a low frequency of treatment-related adverse events, similar to clarithromycin, and an equally low rate of premature discontinuations caused by adverse events, reflecting good tolerance. These findings are consistent with results from a unique phase IV post-marketing surveillance trial to detect adverse events and compromised clinical efficacy in over 15 000 patients with respiratory tract infections who have received gatifloxacin in community-based therapy [23–25].

The growing body of clinical data on the use of gatifloxacin, supported by the results of this phase III study, suggests that it has a place as a first-line agent in the treatment of community-acquired pneumonia. Based on the in-vitro profile and high success rates with penicillin-resistant *S. pneumoniae* in the phase IV post-marketing trial mentioned above, gatifloxacin could be of special interest in countries where multiresistant strains of *S. pneumoniae* are prevalent. Compared with standard agents, which must be administered several times daily, the added convenience of a once-daily dosing schedule may improve patient compliance and reduce the likelihood of resistance developing from sub-optimal antimicrobial dosing. While extensive post-marketing surveillance for adverse events with gatifloxacin continues, evidence to date indicates that gatifloxacin does not cause the phototoxicity, musculo-skeletal disorders, and hepatic and renal problems that have been reported for some of the other broad-spectrum fluoroquinolones [26,27].

Overall, the results of this study demonstrated that gatifloxacin 400 mg once-daily is as safe and effective as clarithromycin 500 mg twice-daily in adult patients with community-acquired pneumonia of typical and atypical aetiology in countries in which pneumococcal resistance to penicillin and/or erythromycin is not yet a concern.

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