A Multicenter Study of Grepafloxacin and Clarithromycin in the Treatment of Patients With Community-Acquired Pneumonia*

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**Study objectives:** To compare the efficacies of 10-day regimens of grepafloxacin (GFX) (Raxar or Vaxar; Glaxo Wellcome; Greenford, UK), 600 mg qd, and clarithromycin (CLA) (Klacid, Biaxin, or Klaracid; Abbott Laboratories; Chicago, IL), 500 mg bid, in patients with community-acquired pneumonia (CAP), on the basis of clinical response, including radiographic evidence, and bacteriologic efficacy.

**Design:** Phase IIIb, double-blind, double-dummy, randomized, prospective, parallel-group, comparative study conducted at 58 centers in 11 countries.

**Patients and setting:** Adult patients with signs and symptoms of CAP that was confirmed by radiographic evidence and who did not require parenteral therapy were included in the study.

**Assessments:** Patients were assessed before treatment, during treatment, after treatment, and at follow-up (28 to 35 days after treatment completion). Clinical response was evaluated. Blood and sputum samples were cultured for bacterial pathogens, and serology testing was performed to detect atypical pneumonia.

**Results:** A total of 504 patients were enrolled into the trial: 251 were randomly assigned to receive GFX and 253 to receive CLA. In patients able to be clinically evaluated, clinical success rates at follow-up were 147 of 163 patients (90%) in the GFX group and 148 of 167 patients (89%) in the CLA group (95% confidence interval, 2±6% to 9%). Pretreatment pathogens were confirmed in 131 of 504 patients (26%), either by culture or serology testing, the primary pathogens being Streptococcus pneumoniae (22%), Haemophilus influenzae (17%), Mycoplasma pneumoniae (25%), and Chlamydia pneumoniae (11%). For patients able to be evaluated who had typical pathogens, bacteriologic success was achieved in 92% of the patients in each treatment group. For patients able to be evaluated who had atypical pathogens, 18 of 18 patients (100%) in the GFX and 23 of 26 patients (88%) in the CLA group had a successful clinical outcome. There were similar rates of adverse events in each group, resulting in ≤7% withdrawal from treatment; gastrointestinal events were the most common.

**Conclusions:** GFX, 600 mg qd, was equivalent to CLA, 500 mg bid, in treating adult patients with CAP. Both treatments were well tolerated.

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**Key words:** atypical pneumonia; clarithromycin; clinical trial; community-acquired pneumonia; C-reactive protein; grepafloxacin

**Abbreviations:** CAP = community-acquired pneumonia; CE = able to be clinically evaluated; CI = confidence interval; CLA = clarithromycin; CRP = C-reactive protein; GFX = grepafloxacin; ITT = intent-to-treat; MCE = able to be microbiologically and clinically evaluated; MITT = microbiologic intent-to-treat

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Community-acquired pneumonia (CAP) remains a common and potentially serious illness, representing one of the most common causes of infection-related mortality worldwide. Clinical diagnostic and radiographic techniques usually cannot differentiate between bacterial and nonbacterial pneumonias but play a role in evaluating severity of illness. Common problems in establishing causes of pneumonia are that 10 to 30% of patients have a nonproductive cough and 15 to 30% receive antibiotic treatment before hospitalization or diagnosis of pneumonia by...

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†A list of participating investigators is given in the Appendix. This research was supported by a research grant from Glaxo Wellcome.

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radiography. Because of the difficulties in establishing the cause of pneumonia, empiric treatment ideally needs to cover all the commonly occurring relevant pathogens.

Pneumonia carries a risk of mortality, and the uncertainty about the severity of the infection means that physicians often prefer to refer patients to the hospital for diagnosis and treatment as a precaution. Morbidity such as dehydration, hypoxemia, and pain will also be considered when deciding whether hospitalization is required. Fine et al have recently defined prediction rules to help in identifying low-risk patients with CAP who may be appropriately treated at home. Simultaneously, a number of newer antimicrobial agents covering a broader spectrum of the key pathogens have become available, extending the choice of oral agents appropriate for pneumonia.

An appreciation of the severity of Legionella pneumophila infection and of the increasing prevalence of Chlamydia and Mycoplasma pneumonias has meant that erythromycin and newer macrolides have been included in CAP regimens for the last 4 to 5 years. The introduction of newer quinolones with enhanced activity against Gram-positive bacteria has added to the antimicrobial armamentarium for pneumonia because these compounds offer comprehensive antimicrobial coverage for all the major pathogens, including intracellular organisms, and provide antibiotic levels after oral administration that are comparable to those achieved with injectable dosing.

Grepafloxacin (GFX) (Raxar or Vaxar; Glaxo Wellcome; Greenford, UK) is a broad-spectrum fluoroquinolone with potent in vitro activity against respiratory pathogens, including Streptococcus pneumoniae, irrespective of penicillin susceptibility, Haemophilus influenzae, Moraxella catarrhalis, and Chlamydia, Mycoplasma, and Legionella species and has a long elimination half-life of approximately 12 h, which allows a once-daily dosing schedule. After oral administration at dosages of 400 mg and 600 mg qd, approximately 80 to 90% of the dose is absorbed independent of food intake and is rapidly and widely distributed into tissues including the respiratory tract, achieving serum levels in excess of the minimal concentration needed to achieve 90% inhibition for important respiratory pathogens. Clinical trials have demonstrated that oral GFX, 600 mg qd, was as effective as amoxicillin, 500 mg tid, in the treatment of CAP and was superior in eradicating pathogens in patients with proven bacterial infection. Clarithromycin (CLA) (Klacid, Biaxin, or克拉地米星; Abbott Laboratories; Chicago, IL) also has proven efficacy against both the atypical and typical pathogens that cause pneumonia.

The current study evaluated the efficacy and safety of 10-day regimens of GFX, 600 mg qd, vs CLA, 500 mg bid, in patients with radiographically documented CAP for whom oral therapy was considered appropriate. It was anticipated at the outset that a proportion of patients would be treated at home, whereas others would be treated in the hospital depending on the standard medical practice in different countries. Clinical evaluations were based principally on the clinical and radiographic response at follow-up (28 to 35 days after treatment completion). Secondary objectives were to compare the bacteriologic efficacy and safety of the two regimens.

Materials and Methods

Patient Population and Study Design

This was a phase IIIb, double-blind, double-dummy, randomized, prospective, parallel-group, comparative study (protocol GFXB3003) conducted at 58 centers in 11 countries (Australia, Canada, Czech Republic, Germany, Italy, Israel, New Zealand, Poland, South Africa, Spain, and Sweden). Regulatory approval was obtained where appropriate, and the study was approved by local ethics committees. Written, informed consent was obtained for each participant in accordance with national guidelines and the Declaration of Helsinki (Hong Kong amendment, 1989).

Patients with chest radiographs taken within 2 days of the start of study medication confirming pulmonary infiltration or consolidation likely to be caused by pneumonia, and patients presenting with one or more of the clinical signs and symptoms consistent with CAP—pleuritic chest pain, cough, fever ($\geq 38^\circ C$), and auscultatory findings such as rales and/or evidence of consolidation—were included in the study. Sputum production was not a requirement for study entry; however, when patients were producing sputum, a sample was collected for culture. Patients could be treated in the community or could be admitted to the hospital, depending on the standard medical practice in different countries.

Patients were excluded if they had nosocomial pneumonia; required immediate IV antibiotic therapy; had received antibiotic therapy within 3 days before study entry; or had bronchial carcinoma, empyema, lung abscess, uncontrolled asthma, pulmonary tuberculosis, or cystic fibrosis. As well as other standard exclusion criteria for clinical trials, patients with an immunocompromised status, malabsorption syndromes, hepatic or renal impairment, and history of seizure disorders were excluded, as were those with known sensitivity to any quinolone or macrolide antibiotic.

Patients were randomized to receive either oral GFX, 600 mg qd for 10 days (251 patients) or oral CLA, 500 mg bid for 10 days (253 patients). In addition to the active medication, patients received concurrent placebo for study-blinding purposes. Administration of additional antimicrobials was not permitted for the duration of the study, and a record was kept of any medication taken concomitantly.

Assessments

After entry into the study and pretreatment assessment, patients were reassessed during treatment (4 to 6 days after treatment initiation), after treatment (1 to 3 days after completion), and at follow-up (28 to 35 days after treatment completion). At each assessment, patients were evaluated for resolution of
signs and symptoms of pneumonia. Before treatment and at follow-up (or withdrawal), chest radiography and physical examinations were performed.

At each assessment, sputum samples were collected (if available) for Gram’s stain, culture, and susceptibility testing (only samples meeting the recognized criteria of ≥ 25 neutrophils and ≤ 10 epithelial cells per low-power field were cultured). Blood was collected for culture at the pretreatment assessment, and if the results were positive or if the subject remained febrile, blood was collected for culture at the posttreatment and follow-up assessments. Primary identification of isolated pathogens was performed using routine laboratory culture methods. Bacterial isolates were tested by disk diffusion for susceptibility to GFX and CLA; in addition, the minimal inhibitory concentration was determined. Production of β-lactamase was determined by the nitrocefin method where appropriate. For S pneumoniae isolates, susceptibility testing to penicillin was performed.

In addition, serology was performed by a central laboratory on pretreatment and follow-up blood or urine samples for detection of the atypical respiratory pathogens Mycoplasma pneumoniae, Chlamydia pneumoniae, and L pneumophila. The presence of Chlamydia and Mycoplasma spp was established using indirect fluorescent antibody assay kits for both IgG and IgM (MRL Diagnostics; Cypress, CA and Zeus Scientific; Raritan, NJ). Tests were interpreted from comparisons of pretreatment and follow-up samples according to the instructions of the manufacturer. At least a fourfold rise in reciprocal value titer for IgG or IgM from pretreatment to follow-up was required to indicate a positive test result. For M pneumoniae, an IgG titer of ≥ 1:128 was required unless a fourfold increase in IgM was also present, when a titer of ≥ 1:64 was acceptable. Legionella spp were detected using radioimmune assays (Bimax; Portland, ME) of urine samples.

C-reactive protein (CRP) determinations were made on blood samples taken before and after treatment to evaluate this test as an additional surrogate marker to indicate the presence of bacterial infection. The number of patients with a CRP value > 50 mg/L at the pretreatment and posttreatment assessments was determined and was also analyzed in conjunction with clinical outcome.

Details of adverse events and any other problems elicited by nonspecific questioning were recorded at each visit.

Efficacy Measures

The primary measure of efficacy was the clinical and radiographic response at follow-up; this was assessed for all patients and for patients with documented infection with either typical or atypical pathogens.

Clinical responses are defined in Table 1.

To grade the clinical outcome, the radiographic response was classified at follow-up as resolved (areas of infiltration or consolidation completely clear), improved (areas of infiltration or consolidation still exist but show evidence of clearing), or unchanged or worse (areas of infiltration or consolidation unchanged or slow evidence of spread or increased density).

Bacteriologic responses are defined in Table 2.

Statistical Analysis

A satisfactory response rate (clinical cure or improvement) of 80 to 89% at follow-up with a broad-spectrum antibiotic was assumed. Assuming an inability to evaluate rate of ≥ 25%, at least 450 patients were required to establish equivalence in both the intent-to-treat (ITT; patients who were randomly assigned and received at least one dose of the study medication) and clinically evaluated populations (eg, patients who were able to be clinically evaluated (CE) in accordance with the study protocol criteria), using a 95% confidence interval (CI) calculated for a two-tailed test of significance at the 15% level with 90% power.2 Equivalence was demonstrated if the lower limit of the 95% CI of the difference in response rate among patients receiving GFX minus the response rate to CLA was > −15%.

Primary efficacy data were analyzed for the ITT and CE populations. Analyses were also performed on the microbiologic intent-to-treat (MITT; patients in the ITT population who had a pathogen isolated on study entry) and the microbiologically and clinically evaluated (MCE; patients in the MITT population who were able to be clinically evaluated) study populations.

RESULTS

Patient Demographics and Disposition

Patients were recruited at 58 centers in 11 countries; 43% of the patients were treated in the community setting (general practice or outpatient clinic), and 57% of patients were hospitalized in accordance with the standard medical management of such patients in different countries.

Patient demographics were similar with respect to age, sex, and ethnic origin between the two study groups (Table 3). The majority of patients, 73%, were ≥ 35 years old, with 23% being ≥ 65 years old. Sixty-two percent of patients had a preexisting medical condition on entry into the study, with cardiovascular (23%) and respiratory (17%) conditions being the most common. The most commonly reported pretreatment symptoms were cough and adventitial sounds, recorded for 95% and 85% of the patients, respectively.

A total of 504 patients were recruited to the study (ITT population), of whom 251 patients were randomized to receive GFX and 253 to receive CLA.

### Table 1—Definitions of Clinical Responses

<table>
<thead>
<tr>
<th>Clinical Responses</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cure</strong></td>
<td>Improvement or resolution of clinical signs and symptoms after treatment and absence, including radiographic evidence, at follow-up</td>
</tr>
<tr>
<td><strong>Improvement</strong></td>
<td>Improvement but incomplete resolution of clinical signs and symptoms, including radiographic evidence, at follow-up</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>No improvement during or after treatment or discontinuation of therapy because of a drug-related adverse event</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>Resolution or improvement after treatment with recurrence of clinical symptoms, including radiographic evidence, at follow-up</td>
</tr>
<tr>
<td>Unable to be evaluated</td>
<td>Significant deviations from protocol</td>
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Clinical Investigations

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There were 106 withdrawals (21%) from the study (51 GFX, 55 CLA; p = 0.78) because of lack of efficacy (4%), adverse events (7%), failure to return for assessment (4%), or other reasons (6%; Fig 1). Compliance was good, with > 99% of urine test results being positive for the presence of antibiotic and 84% of patients taking their medication in accordance with the protocol.

Radiographic findings and the nature and severity of signs and symptoms were comparable in the two treatment groups. At the pretreatment assessment, 78%, 43%, 48%, and 48% of patients reported moderate or severe cough, dyspnea, pleuritic chest pain, and chills, respectively, compared with 3%, 3%, 1%, and 1% of patients at follow-up. No differences were demonstrated between the two treatment groups. Likewise, adventitial sounds, dullness to percussion, friction rub, arthralgia, and myalgia were markedly reduced at follow-up. Sputum was purulent or mucopurulent in 43% of patients at pretreatment and in only 3% of patients at follow-up.

Pretreatment CRP measurements were obtained for 462 patients. A wide range of values was obtained, from 1 to 577 mg/L, with a median of 109 mg/L and SD of 141 mg/L. However, of the 462 patients, 68% had a value > 50 mg/L, suggesting the presence of active infection; values were comparable for the two treatment groups. For the 126 patients in whom a pretreatment pathogen was confirmed and CRP measured, 76% of patients had a value > 50 mg/L. The proportion of patients with a pretreatment value > 50 mg/L was similar for patients with typical and atypical pathogens, although the median value was higher for the former, 171 mg/L compared with 97 mg/L.

Primary Assessment of Clinical Response at the Follow-Up Visit

Assessment of the primary efficacy end point of the study was made using the CE population at follow-up. Clinical signs and symptoms and radiographic evidence were used to assess outcome. Of the 504 patients in the ITT population, 174 (35%) were unable to be clinically evaluated because of a lack of planned posttreatment or follow-up assessments, consumption of prohibited medication, adverse effects unrelated to the study drug, or other significant protocol violations (Fig 1). Thus, 330 patients composed the CE population (163 GFX, 167 CLA). At the follow-up visit, 147 of 163 CE patients (90%) receiving GFX and 148 of 167 CE patients (89%) receiving CLA had a satisfactory clinical response (p = 0.78; 95% CI, −6 to 9%; Fig 2). Hence, formal equivalence was demonstrated between 10-day treatment regimens of GFX, 600 mg qd, and CLA, 500 mg bid, in the treatment of patients with radiographically confirmed CAP. Similarly, equivalence between the two treatment groups was demonstrated in the ITT population, in

<table>
<thead>
<tr>
<th>Bacteriologic Responses</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>Cure</td>
<td>Initial pathogen eradicated</td>
</tr>
<tr>
<td>Presumed cure</td>
<td>Clinical cure or improvement in the absence of sputum or blood culture</td>
</tr>
<tr>
<td>Cure with superinfection</td>
<td>Eradication of initial pathogen with isolation of new organism(s) associated with clinical symptoms of infection</td>
</tr>
<tr>
<td>Cure with colonization</td>
<td>Eradication of initial pathogen with isolation of new nonpathogenic organism(s) not associated with clinical symptoms of infection</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Initial bacteriologic cure with reisolation of original pathogen at follow-up</td>
</tr>
<tr>
<td>Failure</td>
<td>Initial pathogen not eradicated during treatment</td>
</tr>
<tr>
<td>Presumed failure</td>
<td>Clinical failure in the absence of sputum or blood culture</td>
</tr>
<tr>
<td>Failure with superinfection</td>
<td>Initial pathogen not eradicated plus isolation of new pathogen(s)</td>
</tr>
<tr>
<td>Failure with resistance</td>
<td>Initial pathogen(s) developing resistance during therapy</td>
</tr>
<tr>
<td>Unable to be evaluated</td>
<td>Inability to identify or culture pretreatment pathogens, and any other deviation from protocol</td>
</tr>
</tbody>
</table>

Table 2—Definitions of Bacteriologic Responses

<table>
<thead>
<tr>
<th>Table 3—Summary of Demographic and Baseline Characteristics*</th>
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<tbody>
<tr>
<td>Patient Characteristics</td>
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<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Ethnic origin</td>
</tr>
<tr>
<td>Asian</td>
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<tr>
<td>Black</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Height, cm†</td>
</tr>
<tr>
<td>Weight, kg‡</td>
</tr>
</tbody>
</table>

*Values are given as No. (%) and mean ± SD.
†GFX, n = 249; CLA, n = 251.
‡GFX, n = 250; CLA, n = 250.
which 75% and 76% showed a satisfactory response rate for GFX and CLA, respectively (p = 0.88; 95% CI, −9 to 7%; Fig 2).

Clinical equivalence between the GFX and CLA treatment groups was demonstrated in all four study populations. However, some differences in the rates of satisfactory clinical and radiographic response were observed in certain subpopulations of patients able to be evaluated, although these were not statistically significant.

Rates of satisfactory clinical response were slightly better for both GFX and CLA in younger patients, with this age-related difference more apparent in the CLA treatment group. Response rates for patients < 65 years were 93% and 92% for GFX and CLA, respectively; corresponding response rates for patients ≥ 65 years were 81% and 74%. In addition, women treated with GFX had a higher rate of satisfactory clinical response than those treated with CLA (91% vs 85%). No difference was observed in men, with 90% response for each treatment group.

**Posttreatment Assessment of Clinical Response**

The clinical response among the ITT population after treatment was also assessed and was similar in each group, with the proportion of patients assessed as having a satisfactory response (clinical cure or improvement) being 88% and 85% in the GFX and CLA treatment groups, respectively (Table 4). Analysis of the differences between the satisfactory clinical response rates demonstrated equivalence between groups (p = 0.31; 95% CI, −3 to 10%). Analysis of the CE population after treatment showed clinical response rates of 95% and 92% in the GFX and CLA treatment groups, respectively.
Clinical Assessment of Response After Treatment and Follow-Up

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Responses</th>
<th>ITT</th>
<th>p Value</th>
<th>CE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Satisfactory (cure or improvement)</td>
<td>GFX, n = 251</td>
<td>222 (88)</td>
<td>CLA, n = 253</td>
<td>215 (85)</td>
</tr>
<tr>
<td>After treatment</td>
<td>Un satisfactory (failure or unevaluable)</td>
<td>GFX, n = 251</td>
<td>29 (12)</td>
<td>CLA, n = 253</td>
<td>38 (15)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Satisfactory (cure or improvement)</td>
<td>GFX, n = 163</td>
<td>188 (75)</td>
<td>CLA, n = 167</td>
<td>192 (76)</td>
</tr>
<tr>
<td></td>
<td>Un satisfactory (failure or unevaluable)</td>
<td>GFX, n = 163</td>
<td>63 (25)</td>
<td>CLA, n = 167</td>
<td>61 (24)</td>
</tr>
</tbody>
</table>

*Values are No. (%) unless otherwise indicated.

Table 4—Clinical Assessment of Response After Treatment and Follow-Up

distribution comparable with that observed with the ITT population and also demonstrating equivalence between the two treatment groups (p = 0.40; 95% CI, −3 to 9%; Fig 2). Formal statistical equivalence was also established in the MITT and MCE populations.

Posttreatment CRP values were obtained for 444 patients; 413 of these had a satisfactory clinical outcome. For these patients values ranged from 1 to 201 mg/L, with a median of 4 mg/L and SD of 23 mg/L, with only 4% having a CRP value > 50 mg/L. In contrast, for patients who did not have a satisfactory clinical outcome, CRP values ranged from 4 to 377 mg/L, with a median of 74 mg/L and SD of 105 mg/L, with 58% having a CRP value > 50 mg/L. Results were similar for the two treatment groups.

Assessment of Clinical Response in Patients With Confirmed Infection

Patients from whom a pathogen was cultured or who had positive serologic evidence of Legionella, Chlamydia, or Mycoplasma infection responded satisfactorily (MITT population n = 131). Statistical equivalence of satisfactory clinical response incorporating radiographic evidence was demonstrated in this population (p = 0.67; 95% CI, −11 to 20%), with 80% and 76% of patients in the GFX and CLA treatment groups, respectively, classified as cured or improved at follow-up. There was no evidence to suggest that patients with confirmed pathogens on entry into the study had a poorer outcome at follow-up compared with patients for whom no pathogen was detected. Of the 80 patients confirmed as having a typical pathogen before treatment, 30 (75%) in the GFX group and 29 (73%) in the CLA group showed a satisfactory clinical and radiographic response at follow-up. In the CE subpopulation, 23 of 26 patients (88%) responded satisfactorily to GFX compared with 24 of 26 patients (92%) in the CLA group.

In comparison, in the subgroup of patients with atypical pathogens on entry (MITT atypical group n = 57), those treated with GFX showed a higher clinical response rate, 91%, compared with a response rate of 82% (p = 0.58) for those receiving CLA. However, the relatively small sample size means that this difference was not statistically significant. In the CE subpopulation, the trend was similar, with 18 of 18 patients (100%) responding satisfactorily to GFX compared with 23 of 26 patients (88%) responding to CLA (p = 0.39; Fig 2).

For the 126 of 131 patients in whom a pretreatment pathogen was confirmed and CRP measured, 76% of patients had a CRP value > 50 mg/L. Most values were very high (median, 145.5 mg/L). After treatment, in patients with a satisfactory response, the median value fell to 4 mg/L. Patients with an unsatisfactory response maintained a high CRP value with a median of 146 mg/L. Posttreatment results were similar for the two treatment groups and for patients with typical or atypical pretreatment pathogens.

Bacteriologic Response

Most of the assessments of bacteriologic response for patients with typical pathogens were based on either presumed cure or presumed failure, taking into account clinical signs and symptoms. Despite the relatively small numbers of patients, equivalence between the GFX and CLA groups was demonstrated within the MITT population after treatment but with higher response rates obtained for GFX. Of the 40 patients in the typical MITT population receiving GFX, 80% showed a satisfactory response (cure, presumed cure, or cure with colonization) compared with 73% of the 40 patients receiving CLA (p = 0.60; 95% CI, −14 to 29%). In the MCE population, 24 of 26 patients (92%) responded satisfactorily to GFX and 22 of 24 patients (92%) responded to CLA (Fig 2).

Pathogens Isolated and Antibiotic Susceptibility

Pretreatment pathogens were confirmed in 131 patients (MITT population), with typical pathogens isolated in 80 patients (40 GFX, 40 CLA) and atypical pathogens in 57 patients (23 GFX, 34 CLA).
Six patients had both an atypical and a typical pathogen present. Twenty-five bacterial pathogens were isolated from pretreatment blood cultures (11 in the GFX group and 14 in the CLA group) and 67 from sputum (33 in the GFX group and 34 in the CLA group). *S pneumoniae* was the most prevalent organism and was recovered from 15 of 25 blood samples and 18 of 67 sputum samples. The other blood culture isolates were coagulase-negative Staphylococcus spp (five isolates), Streptococcus spp (three isolates), *Proteus mirabilis* (one isolate), and *Escherichia coli* (one isolate).

*S pneumoniae* was the most frequently isolated typical pathogen, followed by *H influenzae* (26 isolates; Fig 3). All isolates were susceptible to the study drugs, correlating with a high number of patients experiencing a satisfactory bacteriologic response rate (cure, presumed cure, and cure with colonization). For patients with *S pneumoniae* isolated from pretreatment blood cultures, seven of eight in the GFX group and six of seven in the CLA group had a successful clinical and radiologic outcome.

Of the patients identified with pathogens on entry into the study, 57 of 131 patients (43%) had an atypical pneumonia attributed to *M pneumoniae* (38 patients), *C pneumoniae* (16 patients), or *L pneumophila* (5 patients). No significant differences were observed in the overall clinical response at follow-up; 18 of 18 CE patients (100%) receiving GFX showed a satisfactory clinical response compared with 23 of 26 CE patients (88%) receiving CLA.

**Safety**

Details of any adverse events were recorded at each assessment (Table 5); the most frequently reported events were GI in nature. The most common events were an abnormal or unusual taste, nausea (which was considered to be a CNS symptom in some patients), diarrhea, dizziness, and vomiting. With the exception of dizziness, which was higher in the GFX group (4% compared with <1% for CLA), the frequency of these events was similar in the two treatment groups. Thirty-three patients experienced serious adverse events, although these events were generally not associated with the study medication (two in the GFX group and five in the CLA group were classified by the investigator as treatment related).

**Table 5—Frequency of Most Common Drug-Related Adverse Effects and Withdrawals in Each Treatment Group**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>GFX, n = 251</th>
<th>CLA, n = 253</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common drug-related adverse events (≥3% occurrence)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal/unusual taste</td>
<td>29 (12)</td>
<td>24 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (10)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (4)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (4)</td>
<td>2 (&lt; 1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Patients withdrawn from entire study because of any adverse event</td>
<td>16 (6)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>Patients withdrawn from treatment because of any adverse event</td>
<td>16 (6)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Patients withdrawn from treatment because of drug-related adverse events</td>
<td>6 (2)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Patients with serious treatment-related adverse events</td>
<td>2 (1)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

*Values are given as No. (%).
Two patients in the GFX treatment group died during the study (one of cor pulmonale, the second of circulatory collapse); both deaths were considered unrelated to treatment by the investigator.

The number of subjects who withdrew from the study (at any time) because of adverse events was 6% for GFX and 9% for CLA (Table 5). The incidence of patients discontinuing treatment because of adverse events was comparable in both treatment groups (≤7%). Six patients (2%) in the GFX group and eight (3%) in the CLA group withdrew because of treatment-related adverse events; of these, none in the GFX group and two in the CLA group were considered serious in nature.

**Discussion**

This study included patients with radiographically documented pneumonia in whom treatment with oral antibiotics was considered appropriate. Forty-three percent of those enrolled in the study were also treated in the community throughout their entire course of treatment. This patient group reflects a group seen usually by primary care physicians but who are frequently referred for hospitalization because of the possible risk of mortality. In some health-care systems, outpatient treatment is becoming increasingly common (70 to 80% in Canada and the United States). With increasing pressures on health-care resources everywhere, the question of which patients require hospitalization and which do not is very pertinent. For the purposes of this study, 57% of those included were treated in the hospital, in part because of the need to collect and document specific information and also reflecting the differences in health-care practice in managing CAP in the 11 countries involved in the study.

Patients were assessed objectively for the severity of the pneumonia according to American Thoracic Society and British Thoracic Society guidelines. Using these guidelines, only 35 patients (7%) were regarded as severe. In a recent report, Fine et al2 regarded all patients with radiographic evidence of pneumonia <50 years of age as low risk group 1. Patients assigned to group 2 are typically middle aged, with a point score of <70, and those assigned to group 3 have coexisting illnesses and a point score of 71 to 90. Although this scoring system was not rigorously applied, the majority of the patients satisfied criteria for inclusion in groups 1 and 2. Coexisting disease or conditions, independently associated with mortality in the study by Fine et al,2 were specific exclusion criteria. A further 14 to 15 patients in each treatment group met the criteria for Fine et al2 group 3. Fine et al2 groups 1, 2, and 3 are regarded as low mortality risk.16

For inclusion into this study, radiographic evidence of CAP was required. Although radiography is a nonspecific method, its use is necessary given that as many as 50% of patients do not present with an identifiable pathogen. Laboratory data (blood and sputum cultures, serology, and other tests such as CRP) often do not give a definitive diagnosis. A positive radiograph is generally accepted in the medical literature for diagnosing pneumonia,11 with few pneumonias lacking a radiographic component.12 However, problems can arise from interpretation differences.13 Radiographic evaluation helps to discriminate between conditions that may mimic pneumonia and may assist in the identification of comorbidities and specific causes, including lung abscess and pulmonary tuberculosis.14 However, the use of both radiography and clinical signs and symptoms does not reliably establish cause in many cases.15 In addition, laboratory data are often negative and results are not usually rapidly available. Consequently, treatment of pneumonia still remains largely empiric. Evaluation of the clinical response of a patient to the chosen antimicrobial agent is clearly of paramount importance, however, and radiographic clearance is dependent on the initial pathogen, the patient’s age, and the presence of comorbidities.16,17 Use of CRP may also prove to be a useful, albeit nonspecific, marker indicating the presence of an infecting agent.

This study, conducted in patients receiving exclusively oral therapy, appears to demonstrate a difference in overall etiologic pattern and frequency of positive blood culture compared with studies of hospital-based CAP, in which *S pneumoniae* usually predominates.18 The microbiologic findings from 500 blood cultures yielded 25 (5%) positive cultures, perhaps indicating the low-risk nature of the majority of these patients. In a study of 517 patients with CAP requiring hospitalization but treated with IV or oral regimens, the positive blood culture rate was 6.6%.19

Atypical pneumonias have generally been reported to occur more frequently in younger patients, with an estimated 25% of CAP cases caused by atypical pathogens,14 and in ambulatory patients, this percentage may be greater. The occurrence of atypical pneumonia in this study was 11% overall, possibly reflecting availability of samples for serology from all patients and also the number of ambulatory patients in the study. In this study, *C pneumoniae* and *S pneumoniae* occurred in 16 and 34 patients, respectively. It has been postulated that *C pneumoniae* may potentiate the severity of pneumococcal infection, emphasizing the importance of treatment covering the atypical pathogens.20,21 Both cases of Legionella...
infection in the GFX-treated group and two of three cases in the CLA-treated group showed radiographic resolution of pneumonia at follow-up. This supports the use of GFX against this potentially dangerous pathogen, given the characteristically rapid progression of this disease. The clinical efficacy of GFX against the intracellular pathogens *M. pneumonieae*, *C. pneumoniae*, and *L. pneumophila* observed in this study correlates well with its *in vitro* activity and penetration into respiratory tissues. Both GFX and CLA penetrate effectively intracellularly, achieving concentrations in macrophages and epithelial lining fluid several times higher than those observed in serum.²²,²³

In general, the incidence of typical bacterial infection was low, with only 94 of 504 patients (18%) having a confirmed pathogen on entry into the study. This is likely to be because of the low number of patients with a productive cough, delays in sample processing because of transportation, and contamination with normal pharyngeal flora.

The overall clinical response in this study was comparable for GFX and CLA, and the results are also comparable with those reported for another broad-spectrum fluoroquinolone, trovafloxacin (200 mg qd).²⁴ Several factors are important in antibiotic selection in patients with CAP, including proven susceptibility *in vitro*, favorable pharmacokinetics, long dosing intervals, minimal monitoring, good safety profile, and low pathogen resistance probability.²⁵ The β-lactams (eg, amoxicillin) are ineffective against *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*, the atypical pathogens isolated in this study. Macrolides such as erythromycin have good activity against these pathogens, but are relatively ineffective against *H. influenzae* *in vitro*. This is overcome to some extent by the new macrolides, including CLA.⁸ However, CLA has a relatively short half-life of 3.8 h compared with the 12-h half-life of GFX. In addition, these long-lived plasma concentrations are achieved, as is the case with most fluoroquinolones, after oral administration of GFX, a route clearly favored for outpatient therapy compared with the IV route, which improves the cost-effectiveness of the therapy. The once daily dosing regimen allowed by the pharmacokinetics of GFX is also a useful aid to compliance and also contributes to increased cost-effectiveness.

In choosing appropriate antibiotic therapy for suspected pneumonia, a number of factors are relevant. Attention should be paid to selection of antibiotic therapy on the basis of risk factors and severity of disease in each patient, including any factors that suggest the presence of an antibiotic-resistant pathogen. Selection of agents that require once or twice daily dosing is also important, because adherence has been shown to be more likely for these dosing regimens.²¹

CRP was measured during the study because this marker has been reported to have diagnostic value in pneumonia, with previous reports indicating that values > 50 mg/L are consistent with bacterial infection.²⁶,²⁷ In this study, there was wide variation in CRP values, but the 50 mg/L cutoff appeared to correlate well with the presence of infection, especially for patients who had serologically or microbiologically proven bacterial infections. The majority of patients had a value > 50 mg/L before treatment; furthermore, most patients with a successful clinical outcome had values < 50 mg/L after treatment, whereas for those with an unsuccessful outcome, the majority still had values > 50 mg/L. Hence, CRP correlates reasonably well with bacterial infection and may also be a useful objective surrogate marker for clinical outcome.

In this study, both antibiotics were well tolerated, with drug-related adverse events accounting for the withdrawal from treatment of ≤ 3% of patients in each group. In a similar study in which CLA was compared with trovafloxacin in the treatment of CAP, treatment withdrawals were 8% in each treatment group.²⁴ As with many antibiotics, the most common adverse events were GI in nature, with nausea and abnormal or unusual taste being the most frequently reported. Similar levels of nausea and abnormal or unusual taste have been reported for other antibiotics such as trovafloxacin (12% nausea) and CLA (19% abnormal or unusual taste).²⁴ Dizziness was reported by 4% of patients treated with GFX compared with 1% of those treated with CLA. In a study comparing trovafloxacin with CLA, dizziness was reported by 10% and 2% of patients, respectively.²⁴ Serious adverse events were rare, and only seven were related to the study medications (two in the GFX group and five in the CLA group). There were two deaths (0.4% mortality rate) in the study. According to the predictions of Fine et al.²,¹⁰ groups 1, 2, and 3 have predicted mortality rates of 0.1%, 0.6%, and 2.8%, respectively. From a retrospective assessment of the patients using the criteria of Fine et al.²,¹⁰ most patients would have been classified in groups 1 or 2 and so a mortality of 0.1 to 0.6% would have been predicted. It was estimated that 35 more-severely ill patients were included in the study, most of whom would have been classified in group 3.

**Conclusion**

Grepafloxacin, 600 mg once daily, was clinically equivalent to clarithromycin, 500 mg twice daily, in
the treatment of CAP. Both agents were given for 10 days. Both agents were well tolerated, with mild GI effects as the most frequently reported adverse events; the frequency of dizziness was slightly higher with GFX. Six percent of patients receiving GFX and 9% given CLA withdrew from the study because of adverse events, with ≤3% of patients in each treatment group discontinuing treatment because of drug-related adverse events. CRP was measured during the study and correlated well with the presence of bacterial infection; this may also be of potential use as a surrogate marker in assessing clinical outcome.

APPENDIX


REFERENCES


