Efficacy and safety of ten day moxifloxacin 400 mg once daily in the treatment of patients with community-acquired pneumonia

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Community-acquired pneumonia (CAP) remains a common and serious illness with approximately 2–4 million cases reported annually. Management of CAP is therapeutically challenging due to the increasing prevalence of penicillin- and macrolide-resistant pneumococci and β-lactamase producing Haemophilus influenzae, as well as the increased recognition of ‘atypical’ pathogens, such as Chlamydia pneumoniae and Mycoplasma pneumoniae, and the frequent need for empiric therapy.

We aimed to evaluate the safety and efficacy of moxifloxacin in the treatment of patients with CAP. To do this we carried out a prospective, uncontrolled, non-blind, Phase III clinical trial, in 27 U.S. centers. Patients included in the study were over 18 years of age with signs and symptoms of CAP confirmed by evidence of a new or progressive infiltrate on chest radiograph. The intervention used was moxifloxacin 400 mg PO once daily for 10 days.

Sputum samples were collected pretherapy for Gram stain and culture for typical organisms. Culture and serological testing for Chlamydia pneumoniae and Mycoplasma pneumoniae was also performed. Susceptibility to moxifloxacin was determined by disk diffusion and MIC. Clinical and bacteriological responses were determined at the end of therapy (0–6 days post-therapy), follow-up (14–35 days post-therapy) and overall (end of therapy plus follow-up). Analyses were performed on both valid for efficacy and intent-to-treat populations. The primary efficacy variable was overall clinical resolution.

Of 254 patients enrolled in the Study, 196 patients were included in the efficacy analyses. The majority of patients were male (58%) and Caucasian (85%) with a mean age of 49 years (range: 18 to 85 years). Only 3% of patients were hospitalized pretherapy. The most common pretherapy organisms identified, by culture or serology, in the valid for efficacy population (i.e. 147 organisms among 116 patients), were: Chlamydia pneumoniae (n=63; 54%), Mycoplasma pneumoniae (n=29; 25%), Streptococcus pneumoniae (n=14; 12%) and Haemophilus influenzae (n=13; 10%). End of therapy, follow-up and overall clinical resolution rates for the valid for efficacy population were 94%, 93% and 93%, respectively. The 95% CI for the overall clinical resolution rate was 88.1%, 95.9%. The overall bacteriological response for patients diagnosed by culture or serological criteria, was 91% (95% CI=84%, 96%). For patients who only met serological criteria for infection, the overall bacteriological response was 94% (60/64). Bacterial response rates for the four most commonly isolated pathogens were: 89% (56/63) for C. pneumoniae, 93% (27/29) for M. pneumoniae, 93% (13/14) for S. pneumoniae and 85% (11/13) for H. influenzae. Drug-related adverse events were reported in 33% (85/254) of moxifloxacin-treated patients. Nausea (9%), diarrhea (6%) and dizziness (4%) were the most commonly reported adverse events.

Atypical organisms were isolated in high frequency among patients with CAP. Moxifloxacin 400 mg once daily for 10 days was effective and well-tolerated in the treatment of these adult patients with CAP. Moxifloxacin offers an effective treatment alternative for CAP due to both typical and atypical bacterial pathogens.

Key words: Chlamydia pneumoniae; community-acquired pneumonia; clinical trial; atypical organisms; moxifloxacin; Mycoplasma pneumoniae.

Introduction

Community-acquired pneumonia (CAP) is a common and serious illness in the U.S.A. with approximately 2–4 million cases of CAP occurring annually, with the majority of patients treated in the outpatient setting (1). At least 10 million physician visits per year are the result of CAP (1).
Although pneumonia is the sixth leading cause of death in the U.S.A. (2) the mortality rate of pneumonia treated in the outpatient setting remains low (1–5%) compared to a rate as high as 25% for patients who require hospitalization (3,4). Of additional significance is a recent retrospective analysis which revealed that $48 billion is spent annually treating CAP patients >65 years of age and $3.6 billion for those less than 65 years of age (5). In Niederman’s survey, annual outpatient costs were $119 million and $266 million, respectively. Consequently, use of effective therapy in the outpatient setting can reduce the overall cost burden for CAP.

A rapid etiological diagnosis is optimal in the management of CAP. However, the pathogen responsible for CAP is not identified in as many as 50% of patients even when extensive diagnostic testing is performed (6,7). In many earlier studies involving adults, Streptococcus pneumoniae was the most commonly isolated pathogen, accounting for up to two-thirds of CAP cases, followed by non-type b Haemophilus influenzae (8). Other less commonly isolated organisms included Staphylococcus aureus, Streptococcus pyogenes, Neisseria meningitidis, Moraxella catarrhalis and Klebsiella pneumoniae (7). In some recent studies, pneumococcus has been recovered less frequently with a concomitant rise in recognition of ‘atyypical’ agents such as Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila (8). The infection rate for these atypical pathogen tend to vary greatly depending upon the patient’s age as well as temporal and geographical patterns (9).

Despite advances in diagnosis and therapy, the management of pneumonia still represents a challenge to the physician. Parallel to the availability of numerous new antimicrobials, bacterial resistance mechanisms have evolved. In the 1990s, pneumococcal resistance to penicillin G and other antimicrobials has increased dramatically, as well as ampicillin resistance due to the increasing prevalence of β-lactamase-producing H. influenzae and M. catarrhalis. Specifically, several studies in the U.S.A. have documented that approximately 40% of H. influenzae and >95% of M. catarrhalis produce β-lactamase enzymes and >20% of S. pneumoniae are highly resistant to penicillin (10–14).

A 1994–1995 survey of 30 U.S. centers reported a penicillin-resistant S. pneumoniae rate of approximately 23% (10). This survey also found 3-4% of pneumococcal isolates to be resistant to cefotaxime and approximately 4-8% of isolates to be resistant to tetracycline and macrolide antimicrobials. In a second survey of penicillin-resistant pneumococcal isolates from the 1995–96 ‘respiratory season’, fluoroquinolones were found to be very active against all isolates of S. pneumoniae (sensitive, intermediate and resistant) (15). In the same study, with the exception of vancomycin and fluoroquinolones, all β-lactams and macrolides tested demonstrated decreased susceptibility with increasing penicillin resistance (16). Another survey conducted by Thornberry et al. 1996–97 reported a further rise in resistance levels with approximately 34% of 9190 pneumococcal isolates penicillin-resistant (17). Importantly, these isolates were collected from adults during the ‘respiratory season’. In the same study, many penicillin-resistant pneumococcal strains showed intermediate or high-level resistance to relatively newer β-lactams and macrolides including amoxicillin-clavulanate, cefuroxime, ceftriaxone and clarithromycin (16). These findings all suggest the need for antimicrobial alternatives for the treatment of respiratory tract pathogens.

The objective of this study was to evaluate the safety and efficacy of moxifloxacin, a new 8-methoxyfluoroquinolone, administered at 400 mg PO once daily for 10 days in the treatment of patients with CAP. Moxifloxacin has excellent in vitro and in vivo animal model activity against the organisms commonly implicated in CAP. For S. pneumoniae, the reported MIC₉₀ for moxifloxacin ranges from 0.12–0.25 μg ml⁻¹, including penicillin-resistant isolates, which is at least four-fold more active than ciprofloxacin (17). The MIC₉₀ values for H. influenzae and M. catarrhalis are each 0.06 μg ml⁻¹ and are not influenced by β-lactamase production (17). Preliminary moxifloxacin data indicate that both Chlamydia and Mycoplasma species are inhibited with an MIC<1–0 μg ml⁻¹ (range of 0.06 to 1.0 μg ml⁻¹) (18). Importantly, single oral moxifloxacin doses have been reported to be safe and well tolerated in Phase I pharmacokinetic studies (19–21).

Methods

STUDY DESIGN AND PATIENTS

We conducted a prospective, open-label, multi-center, Phase III clinical trial of the efficacy and safety of moxifloxacin in the treatment of adult patients with CAP. Patients were given oral moxifloxacin 400 mg daily for 10 days as supplied by Bayer Corporation Pharmaceutical Division, West Haven, CT, U.S.A.

Patients (18 years or older) with CAP documented by the presence of fever and/or elevated white blood cell count (>10 000 mm⁻³) and/or leukocytosis, signs or symptoms of pneumonia [productive cough, purulent sputum, dyspnea or tachypnea (>20 breaths min⁻¹), rigors/chills, pleuritic chest pain, or signs of pulmonary consolidation] and a new or progressive infiltrate on chest radiograph were enrolled. Patients with any of the following characteristics were excluded: allergy to fluoroquinolones; pregnancy or lactation; presence of severe pneumonia requiring parenteral antimicrobials or mechanical ventilatory support; suspected aspiration pneumonia due to vomiting; hospitalization; significant liver or renal impairment or severe heart failure; impaired host defenses (e.g. neutropenia or low CD4 count); history of fluoroquinolone tendinopathy; more than 24 h of systemic antibiotic therapy for the current episode of CAP during study screening or requirement for concomitant antibacterial therapy; rapidly fatal underlying disease; other confounding respiratory disease (e.g. lung cancer); history of prolonged QTc interval or requiring concomitant medication associated with increased QTc interval; administration of another investigational drug within 30 days of study enrollment; or previous enrollment in this study.
The protocol was approved by each institution's internal review board, and written informed consent was obtained from each patient prior to enrollment.

CLINICAL AND LABORATORY EVALUATIONS

Eligible patients were to be evaluated at four visits: pretherapy (within 48 h of first study drug dose), during treatment (days 3–5), at the end of therapy (0–6 days post-therapy) and at follow-up (14–35 days post-therapy) with clinical signs and symptoms noted at each visit. Chest radiographs were obtained at baseline and were repeated at each visit until there was evidence of infiltrate resolution. Blood and urine samples were collected for routine hematological, chemistry coagulation and urinalysis evaluations. In addition, ECGs were performed at the pretherapy and during therapy visits.

Sputum samples were collected at each visit by deep expectoration, as available, and submitted to a local laboratory for Gram stain and culture. Cultures were to be performed on appropriate specimens if the Gram stain revealed \( \leq 10 \) squamous epithelial cells and \( \geq 25 \) leukocytes per low power field. Patients were treated empirically, prior to receipt of culture and susceptibility testing results. If, after treatment had begun, susceptibility test results did not demonstrate the organism to be susceptible to moxifloxacin and the patient was not responding clinically, the investigator had the option of withdrawing the patient from the study. Tentatively, for \( M. \) catarrhalis, \( Haemophilus \) spp and \( S. \) pneumoniae, an MIC of \( \geq 2 \mu g \text{ ml}^{-1} \) and a zone diameter of \( \leq 12 \) mm were considered borderline results for moxifloxacin. Susceptibility testing for moxifloxacin included MIC determinations by standard Etest and Kirby Bauer disk diffusion methods (22). Isolates of \( M. \) catarrhalis and \( Haemophilus \) spp were tested for production of \( \beta \)-lactamase and penicillin susceptibility was determined for \( S. \) pneumoniae isolates.

The following diagnostic tests were performed at the pretherapy visit to identify atypical pathogens. Serum samples were collected for serology (\( C. \) pneumoniae and \( M. \) pneumoniae) at pretherapy, end of therapy and follow-up visits. Serodiagnosis of acute \( C. \) pneumoniae infection was based on an established algorithm that required any one of the following three criteria be satisfied: 1. Four-fold increases in IgG between any two visits, 2. IgM \( \geq 1:32 \) at any visit and 3. IgG \( \geq 1:512 \) at any visit. Serodiagnosis of acute \( M. \) pneumoniae infection was based on an established algorithm that required that any one of the following three criteria; 1. IgM \( \geq 1:10 \) at any visit, 2. four-fold increase in IgG between any two visits and 3. IgG \( < 1:10 \) at pretherapy and \( \geq 1:10 \) at any follow-up visit (27). Serological detection of IgM and IgG antibodies for \( C. \) pneumoniae was by micro-immunofluorescence assay (Chlamydia Research Laboratory, San Francisco, CA, U.S.A.) (27). Serological detection of \( M. \) pneumoniae IgM and IgG antibodies was by enzyme immunoassay (EIA) (Diagnostic Mycoplasma Laboratory, Birmingham, AL, U.S.A.). In addition, one nasopharyngeal specimen was obtained for the isolation of \( C. \) pneumoniae (State U. of New York Health Center, Brooklyn, NY, U.S.A.). Two throat swabs were obtained for the isolation of \( M. \) pneumoniae and if sufficient sputum was available, culture and identification of polymerase chain reaction (PCR) was also performed (Diagnostic Mycoplasma Laboratory). \( L. \) pneumophila was to be identified using a urinary antigen EIA and a sputum culture.

EFFICACY ENDPOINTS

The effectiveness of the study drug was determined by assessing the patients' clinical response and the presumed or documented bacteriological response of the infecting organism. Clinical response was determined by the investigator based on assessment of signs and symptoms of pneumonia at the end of therapy (0–6 days after last dose of study drug) and follow-up (14–35 days after last dose of study drug) visits.

The bacteriological response was defined as eradication when the initial pathogen was absent after treatment or at follow-up, and was defined as persistence when the initial pathogen remained after treatment regardless of clinical response. In many cases, a post-treatment sputum specimen was not available because of resolution of productive cough and the bacteriological response was considered to be presumed eradication or presumed persistence as determined by clinical response.

All patients receiving the study drug for any length of time were evaluated for drug safety (intent-to-treat population). Safety of study drug therapy was monitored by clinical observations and by conventional laboratory tests as described above. Adverse events were rated by the investigator as to their severity (mild, moderate, severe), and by the relationship to the study drug (probable, possible, remote, or none).

In addition to the primary analysis of the valid for efficacy population (i.e. patients with or without a pretherapy pathogen), additional analyses were performed for the population considered to be clinically and bacteriologically valid (i.e. all patients with a pretherapy pathogen) and for the intent-to-treat population (i.e. all patients who received at least one dose of study drug).

STATISTICAL ANALYSIS

To be considered valid for efficacy, the patients must have met protocol criteria for CAP, not have protocol violations influencing efficacy have been compliant with study medication for at least 5 consecutive days (unless a treatment failure) and have a follow-up clinical assessment at least 14 days after completing therapy (unless a failure).

Statistical analyses were performed to determine the clinical response in the valid for efficacy population and the intent-to-treat population. The intent-to-treat population was defined as all patients who received at least one dose of study drug. The primary efficacy variable in this study was the overall clinical response (Table 1).
Patients had to receive at least 2 days of therapy to be considered a failure and at least 5 days of therapy to be considered a success. All failure assessments were carried forward. A more detailed definition of clinical response categories is provided in Table 4.

Secondary efficacy parameters included overall bacteriological response, as well as bacteriological and clinical responses at end of therapy. A two-sided 95% confidence interval (CI) was constructed around the mean clinical success rate using a normal approximation with continuity correction as described in Fleiss (23).

Statistical summaries were provided for demographic and baseline characteristics, including means, standard deviations, medians and quartiles for quantitative data, or frequency counts for categorical data.

Safety analyses included tabulations of type, frequency, duration and drug relatedness of treatment-emergent events. In addition, laboratory data were analyzed using descriptive statistics and values occurring outside of normal ranges were identified.

Results

Two hundred and fifty-four patients were enrolled from 27 medical centers between December 1996 and May 1998 from multiple geographical areas of the U.S.A. All patients received at least one dose of the study drug and were thereby included in the intent-to-treat population. The primary valid for efficacy population for overall clinical response consisted of 196 (77%) patients. One hundred and sixteen (46%) patients were valid for efficacy and were considered microbiologically-valid because of identification of causative pathogens by culture or serology.

Fifty-eight patients (23%) were excluded from the efficacy analysis. The primary reasons for exclusion were insufficient duration of therapy (n=14), violation of inclusion/exclusion criteria (n=12) and missing or invalid efficacy data for the primary time point (n=11). The inclusion/exclusion violations were lack of an abnormal chest radiograph at pretherapy consistent with pneumonia (n=6), insufficient pneumonia symptoms at entry (n=3) and presence of lung cancer or neutropenia (n=3). Twenty-six patients were discontinued from the study prematurely. The most frequent reasons for early discontinuation included adverse events [n=18 (see safety below)] and protocol violations (n=7). Ten patients were hospitalized after the start of therapy, only five of which were valid for efficacy.

The baseline demographic and medical characteristics for the overall clinical valid for efficacy population are summarized in Table 2. Among 196 patients, the majority were male (58%) and Caucasian (85%) with a mean age of 49 years. Less than 3% of patients were hospitalized prior to receiving study drug therapy. Smoking history (current or past) was reported by more than half of valid for efficacy patients. Pretherapy antibacterials were taken by 19 of 196 (10%) patients. The pretherapy symptoms reported included 80% of patients with rigors/chills, 99% with cough and 61% with pleuritic chest pain. The prevalence of the following signs at presentation was reported for the valid for efficacy population: rales (72%) ronchi (72%) and dullness to percussion (39%).

PRETHERAPY CAUSATIVE ORGANISMS

A total of 147 of 254 (58%) enrolled patients had 190 organisms identified by either serological or culture methods. One hundred and forty-seven pathogens were identified from 59% (116 of 196) of patients who were valid for efficacy.

Pretherapy causative organisms, by culture or serological criteria, for the valid for efficacy group are outlined in Table 3. Among the 116 patients with pretherapy organisms, 61 were identified by serology only, 74 by culture, with or without serology, and 19 by both methods. C. pneumoniae was the most frequently identified organism.
(63/116 patients; 54%) followed by M. pneumoniae (29/116 patients; 25%). The most frequently isolated typical respiratory tract pathogens were S. pneumoniae (14/116 patients; 12%) and H. influenzae (13/116 patients; 11%). Of the 63 patients considered to have causative C. pneumoniae by either method, three had both positive serology and a causative pretherapy C. pneumoniae culture isolate, 57 had only positive serology and three had only positive pretherapy culture. Of the 29 patients considered to have causative M. pneumoniae, 14 had both positive serology and a causative pretherapy M. pneumoniae culture isolate, seven had only positive serology and eight had only positive pretherapy culture.

Clinical response

Among 196 patients who made up the primary efficacy population, the overall clinical resolution rate was approximately 93% (95% CI=88%, 96%). Similar rates were found at the end of therapy and follow-up visits (Table 4). Among the 212 patients who were valid at the end of therapy time point, clinical resolution was 97% (95% CI=94%, 99%). For the microbiologically valid population, a clinical resolution rate was observed in 110 of 116 patients (95%), including the one patient with a penicillin-resistant pathogen at study entry. For patients with CAP due to atypical organisms, the clinical resolution rate was

### Table 3. Causative organisms at pretherapy as determined by serological criteria for acute infection or culture*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Culture-positive</th>
<th>Serology only</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>n=61</td>
</tr>
<tr>
<td>Chlamydia pneumoniae †</td>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae †</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>NA</td>
<td>14</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>NA</td>
<td>9</td>
</tr>
</tbody>
</table>

*More than one organism was considered causative for several patients.
†Three patients met serological criteria for both C. pneumoniae and M. pneumoniae infection. Patient A: *Chlamydia* titers were 1:128 (IgM) and 1:256 (IgG) post-therapy vs. not detectable at baseline; *Mycoplasma* titers were 1:640 (IgM) and 1:80 (IgG) at end of therapy and 1:160 (IgM) and 1:10 (IgG) post therapy vs. not detectable at baseline. Patient B: *Chlamydia* titers were 1:512 (IgG) post therapy vs. 1:256 (IgG) baseline; *Mycoplasma* titers were 1:40 (IgG) at end of therapy and 1:20 (IgG) post therapy. In patient B, IgM titers were not detectable for both pathogens at all time points. Patient C: *Chlamydia* titers were 1:16 (IgM) and 1:512 (IgG) post therapy vs. 1:64 (IgM) and 1:512 (IgG) baseline; *Mycoplasma* titers were not detectable (IgG and IgM each <1:10) at all time points except for an IgM titer of 1:20 at baseline and an IgG titer of 1:10 at end of therapy. NA: not applicable.

### Table 4. Clinical responses at end of therapy, follow-up and overall

<table>
<thead>
<tr>
<th></th>
<th>Moxifloxacin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=196)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>End of Therapy (0–6 days post-therapy)</td>
<td>Resolution 184 (96.8)</td>
</tr>
<tr>
<td></td>
<td>Failure 6 (3.2)</td>
</tr>
<tr>
<td>Follow-up (14–35 days post-therapy)</td>
<td>Continued resolution 182 (95.8)</td>
</tr>
<tr>
<td></td>
<td>Failure 2 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Relapse 6 (3.2)</td>
</tr>
<tr>
<td>Overall †</td>
<td>Resolution 182 (92.9)</td>
</tr>
<tr>
<td></td>
<td>Failure 14 (7.1)</td>
</tr>
</tbody>
</table>

*Indeterminate responses were excluded. Clinical Response Definitions: resolution (clinical cure defined as disappearance or sufficient improvement in pneumonia signs/symptoms such that additional or alternative antimicrobial therapy was not required); failure (insufficient lessening of signs/symptoms requiring additional or alternative antimicrobial therapy); continued resolution (continued clinical cure as defined above); relapse (reappearance of signs and symptoms at follow-up visit). Indeterminate clinical responses 95% CI=88.1%, 95.9%.
Patients infected only with typical organisms had a 100% clinical resolution rate. Clinical resolution was >90% for all demographic and medical characteristics subgroups, except for those of Hispanic origin (82%) and patients >45 years of age (89%). For the intent-to-treat population, the overall clinical resolution rate was identical to that of the efficacy valid group (93%; 95% CI=89%, 96%).

**Bacteriologic response by patients**

The overall bacteriological eradication rate for patients with either serological or culture-proven infection (combining end of therapy and follow-up responses) was 91% (106 of 116) (95% CI=84%, 96%). Of the 10 patients categorized as bacteriological failures at the follow-up visit, three had persistent positive cultures (two C. pneumoniae, one M. pneumoniae), six were determined to have presumed persistence due to clinical failure, and one had recurrence with two organisms cultured (H. influenzae and E. coli). Excluding patients who only met serological criteria, the overall bacteriological response was 94% (60/64).

Overall bacteriological response rates for the intent-to-treat population were also consistent with those of the valid for efficacy population (92%; 113 of 123) (95% CI=85%, 96%).

**Bacteriologic response by organism**

The overall bacteriological responses for each of the causative organisms at the end of therapy (including patients who only met serological criteria for microbiologically documented infection) are outlined in Table 5 for the valid for efficacy population. The bacteriological response was 93% each for M. pneumoniae and S. pneumoniae, 89% each for C. pneumoniae and S. aureus, and 85% for H. influenzae. The eradication rates for C. pneumoniae and M. pneumoniae infections with pretherapy positive cultures only were 67% (4/6) and 95% (21/22), respectively.

### SAFETY AND TOLERABILITY

Among 254 patients in the intent-to-treat population, 89% received moxifloxacin for a total of 9–11 days. Eighteen patients (7%) had the study drug discontinued prematurely because of an adverse event (see Table 6). Two patients each were discontinued for nausea, diarrhea, asthma and rash. No other adverse events resulted in discontinuation of more than one patient.

One hundred and twenty-two patients (48%) experienced a treatment-emergent adverse event. Nausea (10%), diarrhea (8%) and dizziness (6%) were the most commonly reported treatment-emergent events. C. difficile studies were not routinely performed for patients who experienced diarrhea. The majority of adverse events were considered mild (44%) or moderate (34%) in intensity. Most adverse events resolved during the course of the study (88%).

Any drug-related adverse event was reported by the investigator in 85 (33%) patients. Gastrointestinal-related events were the most frequently reported drug-related events (nausea, 9% and diarrhea, 6%) followed by drug-related central nervous system event (dizziness, 4% and insomnia, 2%). Rates of drug-related rash were low (2%). Photosensitivity was not reported in any treated patients.

### Discussion

This prospective, open-label multi-center study confirmed that moxifloxacin 400 mg once daily for 10 days is a safe and effective once daily oral treatment for patients with CAP. The overall clinical and bacteriological response rates were 93% and 91%, respectively. Clinical success was excellent in patients with both typical and atypical
pathogens. The clinical success rate was somewhat higher for patients with typical pathogens (100%) compared to those with atypical pathogens (93%), although this difference was not statistically significant. The bacteriological response for individual respiratory tract pathogens was comparable to the overall bacteriological response for culture isolates and serologically confirmed pathogens indicating that moxifloxacin is effective in eradicating typical and atypical pathogens that commonly cause CAP.

As reported by others (6,7), slightly more than half (58%) of the patients enrolled in the current trial had a bacterial pathogen identified by culture or serology. However, in contrast to earlier reports, S. pneumoniae was isolated in only 8.4% of patients in the study (6,7). The low rate of pneumococcal infection may be explained by the relatively young age of patients enrolled in the current trial (49 years) and the fact that patients with other serious debilitating diseases or risk factors were excluded from the study (e.g. nursing home residents). Another possible reason is that the standard diagnostic techniques for identifying the pneumococcus from expectorated sputum lack sensitivity and specificity due to prior antibiotic exposure, poor-quality specimens and delays in processing (7). However, few patients in this trial received prior antibiotics and sputum specimens were evaluated with a Gram stain to determine the quality of the specimen. C. pneumoniae and M. pneumoniae were the most commonly identified bacteria in this study, 45% and 18%, respectively. The incidence of Mycoplasma pneumoniae as confirmed by serology was similar to that reported in the literature (10–20%) (9,24,25). However, the 45% incidence of Chlamydia pneumoniae as confirmed by serology and/or culture tended to be higher than most previous studies of CAP (24,25). In several studies conducted over the last decade in ambulatory patients with CAP, the frequency of serodiagnosis of C. pneumoniae was reported to range from 10–20% (9,24,25). The extensive efforts to identify C. pneumoniae in this trial may explain the higher rates of isolation. We should add that one site, which recruited 20 patients, saw no cases of C. pneumoniae or M. pneumoniae, which is suggestive of geographical variation. Moreover, one site in Spokane, WA, U.S.A. and one site in Boise, ID, U.S.A. did report a higher proportion of patients with C. pneumoniae infection than did other sites.

The prevalence of Chlamydia pneumoniae in clinical studies may vary depending on the culture or serological methods employed and the patient population studied (9,26,27). In the present study, the mean age of patients with Chlamydia pneumoniae identified was 49, the same as the overall mean age. Serodiagnosis of C. pneumoniae was based on an established algorithm which required that one of the following three criteria be satisfied: 1. Four-fold increase in IgG between any two visits, 2. IgM≥1:32 at any visit and 3. IgG≥1:512 at any visit. It is recognized that the most rigorous and specific criterion is demonstration of a 4-fold increase in IgG titer, and that the least rigorous and specific criterion is single high-titer elevation of IgG (IgG≥1:512). While the algorithm described above is frequently used, in some reports, high-titer IgG elevations are not included in the diagnostic criteria for acute C. pneumoniae infection (27). It is possible that many of the single high-titer elevations of IgG in our patients were indicative of previous of chronic infection with C. pneumoniae. However 17 of 60 patients who met the serological criteria for C. pneumoniae elevation had IgM titers≥1:32 at any visit, a finding consistent with acute infection. In addition, 10 of 60 patients that met the overall serological criteria for C. pneumoniae also had a 4-fold increase in IgG titer while three patients who met the overall serological criteria also had positive Chlamydia cultures. To confirm the IgM findings, serological testing for IgM C. pneumoniae antibodies was repeated using the sera from 20 patients with detectable IgM titer, with and without rheumatoid factor absorption (28). IgM titers on repeat micro-immunofluorescence testing after rheumatoid factor absorption were similar to those originally reported. Most patients had a significant change in IgM titer rheumatoid factor absorption; IgM titers after rheumatoid factor absorption were less than 1:32 in sera from two of 15 patients reported as≥1:32 (original and repeat testing without rheumatoid factor absorption).

Although special culture techniques are available for M. pneumoniae and C. pneumoniae, few laboratories routinely cultivate for the these pathogens in the clinical setting. Accordingly, the true prevalence of these latter atypical pathogens is not well known because of limitations in diagnostic sensitivity, specificity and availability. The current trial stresses the importance of using empiric therapy with reliable atypical coverage when treating patients with CAP and the need for continued surveillance for atypical pathogens as important causes of CAP.

The exponential growth of bacterial resistance in the U.S.A. will ultimately lead to increased healthcare costs, namely due to the increased chance that initial empiric antimicrobial therapy will be inappropriate, ultimately resulting in increased hospital admissions or an increased length of hospital stay. Although pharmaco-economic data were not collected in the current trial, treatment with moxifloxacin provided high clinical and bacteriological success rates. The clinical and economic benefits of moxifloxacin compared to other standard β-lactam or macrolide antimicrobials remains to be evaluated in large controlled trials in patients with CAP stratified by comorbidities.

In this first non-comparative CAP clinical trial with moxifloxacin, the quinolone was found to be safe and well tolerated. As reported for other available fluoroquinolones, nausea, diarrhea and dizziness were the most commonly reported drug-related events, occurring in 9%, 6% and 4% of patients, respectively. It is worth emphasizing, however that only two patients were discontinued for nausea and diarrhea, and only one patient for dizziness. In addition, photosensitivity was not reported for any patient during the trial's surveillance period. Most of the adverse events reported were mild to moderate in intensity and resolved without medical intervention.

The selection of an empiric therapy for the treatment of patients with CAP is not always a straightforward decision for the clinician. In the majority of cases, initial empiric therapy is, by necessity, broad in spectrum. If the patient
can be managed in the outpatient setting, oral therapy that is convenient (e.g. once a day), safe, lacking in clinically significant drug interactions and capable of eradicating both typical and atypical pathogens is desirable. Appropriate modifications of therapy can subsequently be made based upon the patient’s clinical progress and available microbiological data. Newer fluoroquinolones with expanded Gram-positive activity have recently been recommended by the Infectious Disease Society of America as empiric agents for treatment of CAP, especially as resistance to β-lactams and macrolides becomes more prevalent (7). In summary, moxifloxacin was found in this trial to be an effective and safe treatment for CAP with excellent in vivo activity against typical, including Gram-positive organisms, and atypical respiratory pathogens. Moxifloxacin is an attractive treatment alternative for patients with CAP who qualify for oral anti-infective therapy and offers the convenience of once a day dosing.

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References

17. Brueggeamb AB, Kugler KC, Doern GV. In vitro activity of BAY 12-8039, a novel 8-methoxyquinolone,


21. Stass H, Kubitza, Schühly U, Wingender W. Pharmacokinetics (PK) and Safety (S) and Tolerability (T) of 800 mg BAY 12-8039 (BA) administered orally as a single dose. Presented at the 8th European Congress of Clinical Microbiology and Infectious Diseases, Lusanne, Switzerland, May 25–28, 1997, abstract P338, p. 87.


