A Comparison of Moxifloxacin and Azithromycin in the Treatment of Acute Exacerbations of Chronic Bronchitis

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- Objective: To compare the efficacy, safety, and patient-reported effectiveness of short-course moxifloxacin versus azithromycin for the management of acute exacerbation of chronic bronchitis (AECB) in a primary care setting.
- Design: Prospective, multicenter, nonblinded, phase IIb clinical trial.
- Participants: 401 adult patients with signs and symptoms of AECB.
- Intervention: Patients randomly received a 5-day oral regimen of either moxifloxacin (400 mg once-daily) or azithromycin (500 mg on day 1, and 250 mg once daily for 4 days).
- Outcome measures: Rate of clinical success at follow-up 14 to 21 days after completion of therapy. Patient-reported responses to therapy (time to symptom relief and resumption of normal activities) were assessed by questionnaire. Drug-related adverse events were also assessed.
- Results: Clinical resolution at 14 to 21 days was 85% for moxifloxacin- and 81% for azithromycin-treated patients (95% confidence interval, -6.0% to 14.0%). Drug-related adverse events reported in the moxifloxacin and azithromycin groups were 12% and 9%. Patients in the moxifloxacin group reported feeling better significantly faster than did patients in the azithromycin group (P = 0.0236). More moxifloxacin-treated patients (40%; 71 of 176) reported symptomatic relief by day 3 than did azithromycin-treated patients (27%; 45 of 165) (P = 0.012). More moxifloxacin-treated patients (36%; 58 of 163) reported a return to normal activities within 3 days of therapy than did azithromycin-treated patients (26%; 41 of 159). No significant differences were observed in average work time lost.
- Conclusions: Short-course moxifloxacin was as effective and safe as azithromycin in the treatment of AECB. Patients treated with moxifloxacin reported faster symptom relief and returned to normal activities more rapidly.

Acute exacerbation of chronic bronchitis (AECB) is a common respiratory condition associated with substantial patient morbidity. Approximately 50% of patients who experience acute exacerbations report at least 2 episodes per year [1,2]. More than 12 million outpatient physician visits are related to AECB. Twenty percent of patients with AECB will require hospitalization due to the development of pneumonia and/or respiratory insufficiency [1–3].

Most patients experiencing an exacerbation consult a primary care physician and are prescribed antibiotic therapy. Bacterial cultures generally are not performed due to the time, expense, and difficulty of obtaining uncontaminated bronchial sputum samples in the primary care setting. Although bacteriologic eradication is an important marker of overall antimicrobial efficacy, a quick return to work or other activities as reported by patients is also a clinically important outcome.

The Moxifloxacin Therapeutic Circles program was initiated to provide a clinically relevant practice perspective on the treatment of AECB. This trial, which was conducted exclusively in the primary care setting, compared moxifloxacin and azithromycin for the treatment of AECB. Although clinical efficacy was the primary outcome of interest in this study, patient-reported outcomes were also assessed. The trial attempted to simulate actual clinical practice conditions; accordingly, bacteriologic assessments and follow-up cultures were not conducted, reflecting an empiric approach to treatment.

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MOXIFLOXACIN AND AZITHROMYCIN

Methods

Patients
Between September 1999 and May 2000, 401 patients were enrolled in this open-label study conducted in 74 primary care practice sites throughout the United States. Male or nonpregnant female outpatients at least 18 years old with clinically documented AECB of suspected bacterial origin and without a recent chest x-ray suggestive of a new pneumonia or lobar consolidation were eligible. Underlying chronic bronchitis was defined as the daily production of sputum on most days for at least 3 consecutive months and for more than 2 consecutive years. Patients were included in the study if they had symptoms of increased sputum purulence and at least 1 of the following: increased sputum volume, increased cough, or increased dyspnea or fever (>38°C orally). Patients were excluded from enrollment if they had a severe respiratory exacerbation; were allergic to carboxyquinolone derivatives or azalide/macrolide derivatives; had previous history of fluoroquinolone-related tendonopathy; were unable to take oral medication; were pregnant or lactating; had a recent diagnosis (<5 years) of unresolved lung or chest cavity malignancy, active tuberculosis, cystic fibrosis, or significant bronchiectasis; had a neutrophil count <1000/mm³, CD4 cell count <200/mm³, or other evidence of significant immunosuppression; had evidence of significant liver impairment (aspartate aminotransferase, alanine aminotransferase, or total bilirubin >3 times upper limit of normal); had renal insufficiency requiring dialysis; history of inherited or sporadic syndromes of QTc prolongation; needed a concomitant antibacterial agent with a spectrum of activity similar to the study drugs; received drugs known to affect QT interval (eg, amiodarone, sotalol, terfenadine); or received previous therapy with a systemic antibiotic for more than 24 hours prior to enrollment, unless a treatment failure. Patients were randomized by computer code in a 1:1 ratio to receive a 5-day oral regimen of either moxifloxacin (400 mg once daily) or azithromycin (500 mg on the first day of therapy and then 250 mg once daily for 4 days).

The trial protocol was reviewed and approved by each investigator’s independent ethics committee, and informed consent was obtained from each patient prior to enrollment in the study.

Outcome Measures
All patients receiving at least 1 dose of study drug (the intent-to-treat population) were evaluated for clinical response at the test-of-cure visit (14 to 21 days after completion of therapy). Clinical response was based on patient examination using the following parameters: objective signs of auscultatory findings (rales, rhonchi, wheezing, breath sounds); prolongation of expiratory phase; presence of fever >38°C; white blood cell (WBC) count >12,000 cells/mm³; subjective symptoms of chest pain or discomfort; change in cough frequency and severity; sputum characteristics (thickness and volume); and dyspnea. Clinical response was graded as clinical resolution (disappearance of acute signs and symptoms related to the infection or sufficient improvement such that additional or alternative antimicrobial therapy was not required), clinical failure (insufficient lessening of the signs and symptoms of infection such that additional or alternative antimicrobial therapy was required), or indeterminate (clinical assessment was not possible for any reason). Safety was assessed on the basis of investigator-determined drug-related adverse events defined by COSTART terminology [4].

Patient-reported outcomes were assessed during the test-of-cure visit using a series of 5 questions:

- When did the patient begin to feel better (ie, symptom relief) after start of treatment?
- When did the patient begin to return to normal activity?
- Was the dosing schedule easy to understand?
- Does the patient work for pay?
- How many hours of work (from the start of treatment) did the patient miss due to illness?

Statistical Analysis
The attained sample size of 355 responses (excluding indeterminate responses) was sufficient to provide greater than 85% power for testing the null hypothesis of inferiority of moxifloxacin to azithromycin at the 0.05 level with a lower limit of noninferiority of 10% and predicted success rates of 90% in each group.

For each evaluation of clinical response, a 2-sided 95% confidence interval (CI) for the weighted difference between treatment groups was constructed using Mantel-Haenszel weights (weighting by center). Equivalence was defined as the lower limit of the 2-sided 95% CI for the difference between groups being greater than –10%. Patient-reported outcomes data were evaluated using the Wilcoxon test and the Fisher’s exact test (both 2-sided). Significance was defined as P<0.05.

Results

Clinical Outcomes
A total of 203 patients were randomized to the moxifloxacin regimen and 198 to the azithromycin regimen. Of these, 201 patients received at least 1 dose of moxifloxacin and 198 received at least 1 dose of azithromycin. The 2 treatment groups were well matched with respect to demographic variables, although a higher proportion of moxifloxacin-treated patients had a history of smoking (Table 1).
At least 94% of patients completed the full course of therapy (193 moxifloxacin, 186 azithromycin); the rate of premature discontinuation was similar between treatment groups (5% moxifloxacin, 6% azithromycin) and was primarily due to inadequate therapeutic effect. In the intent-to-treat population, there were 22 indeterminate responses in each group. Excluding these responses, clinical resolution at the test-of-cure visit was 85% (152/179) for moxifloxacin and 81% (143/176) for azithromycin (95% CI, –6.0% to 14.0%). The incidence of drug-related events was 12% in the moxifloxacin group and 9% in the azithromycin group (Table 2). Premature discontinuation due to drug-related adverse events was ≤1% in both groups.

Patient-Reported Outcomes
The number of patient responses was less than the total intent-to-treat population due to missing or indeterminate data. Regarding the intent-to-treat population, 40% (71 of 176) of patients who received moxifloxacin and 27% (45 of 165) of those receiving azithromycin subjectively reported an improvement in their bronchitis within 1 to 3 days of initiation of therapy (Figure). The mean time to patient-reported symptom relief was 5.1 days for moxifloxacin versus 5.8 days for azithromycin. This difference was not statistically significant using the Student’s t-test but was significant at the 0.05 level (P = 0.0236) using the more appropriate 2-sided Wilcoxon test.

Ninety percent (64 of 71) of moxifloxacin- and 93% (42 of 45) of azithromycin-treated patients who reported symptom relief by day 3 of treatment went on to become clinical successes (resolution of symptoms). A higher percentage of moxifloxacin-treated patients (36%; 58 of 163) reported resuming normal activities within the first 3 days of therapy than did azithromycin-treated patients (26%; 41 of 159).

In the per-protocol population, a higher percentage of patients treated with moxifloxacin reported symptomatic improvement (39%; 49/127) and return to normal activity within 3 days of therapy initiation (35%; 41/118) than did patients receiving azithromycin (31%; 39/127; 28%, 34/123). These differences were not statistically significant. The per-protocol population included all patients with no major protocol violation who had (1) received a study antibiotic for at least 72 hours if a clinical failure, (2) completed the test-of-cure evaluation at post-therapy days 14 through 21, and (3) had been at least 80% compliant (assessed by pill count) with the study drug regimen.

An equal proportion of patients from each group (48%) indicated working for pay. The total amount of work time lost is shown in Table 3. There were no statistically significant differences in terms of the average amount of work time lost (12 hours for moxifloxacin group versus 11 hours for azithromycin)
Both groups were similar when comparing lost work time of > 1 to 2 days and > 3 days, but moxifloxacin-treated patients indicated missing 1 to 8 hours half as often (8%) as those receiving azithromycin (17%). At least 90% of patients from each treatment group reported understanding the dosing regimens.

**Discussion**

The moxifloxacin and azithromycin regimens used in this study for the treatment of AECB were shown to be equivalent in terms of clinical response at the test-of-cure visit and incidence of drug-related adverse events. Overall patient-reported outcomes were similar in the treatment groups; however, patients receiving moxifloxacin had more rapid resolution of their infection. Specifically, by day 3 of therapy, significantly more moxifloxacin-treated patients (40%) reported that their condition had improved than did azithromycin-treated patients (27%). This trend toward a faster rate of improvement with moxifloxacin is consistent with a larger proportion moxifloxacin patients reporting return to normal activity within 3 days of therapy.

Although the statistical significance of these data must be interpreted cautiously considering the retrospective determination of analyzed time interval, the choice of a 3-day analysis is reasonable given the bacteriologic eradication data shown by DeAbate and colleagues [5]. In this study, eradication of the original causative organism was higher by day 3 in the moxifloxacin group (63%) than in the azithromycin group (48%). This earlier study, however, did not examine or report any meaningful differences in the time to improvement of symptoms. In the current study, it is noteworthy that 90% of moxifloxacin-treated patients who reported symptomatic relief by day 3 were categorized by their primary care physician at the test-of-cure visit as having clinical resolution of infection. The corresponding rate for the azithromycin group was 93%. These data further suggest that the outcome measure of “time to symptomatic improvement on day 3” has validity.

The significance of the lost work time data is unclear. It was interesting that among patients who were actively working for pay, nearly twice as many azithromycin-treated patients compared to moxifloxacin-treated patients reported missing 1 to 8 hours of work, presumably as a result of their

**Figure.** Patient-reported therapy outcomes at the test-of-cure visit (14 to 21 days after completion of therapy). Data are expressed as the cumulative percentage of all patients’ responses for each time interval. *P = 0.012 using Fisher’s exact test (2-tailed); NS = P = 0.07 (2-tailed).
illness. Considering that other captured time intervals (ie, 9 to 16, and 17 to 24 hours) were nearly equivalent between treatment groups, the disparity between treatments shown for the 1 to 8 hour interval may suggest up to a 1-day difference in patient response for a percentage of patients. This concept is not unrealistic considering the aforementioned outcome results for symptom relief and time to return to normal activities.

The interpretation of this study may be limited by the open-label design and lack of confirmative bacteriologic analyses. Furthermore, the subjective nature of the patient responses could be influenced by interpretation bias. However, the intention of this trial was not only to compare clinical efficacy and safety of moxifloxacin and azithromycin in the treatment of AECB, but also to reflect a true primary care approach to community-based patients with AECB in a less protocol-driven manner. The determination of a chosen treatment option’s success or failure is most often based on clinical judgment in the office and on whether the patient communicates to his or her physician whether the prescribed drug worked. This analysis provides some insight into potential differences between treatment drugs not only in terms of clinical response rates but also in terms of patient-reported outcomes. The ability of an antibiotic to more rapidly improve a patient’s symptoms, thereby permitting the patient to return to work or resume normal activities faster, should be considered in the selection of empiric therapy. Moreover, more rapid patient improvement is important in reducing morbidity and mortality in patients presenting with comorbid disease. The potential for faster clinical improvement suggested by this study has socioeconomic implications and warrants further investigation.

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Therapeutic Circles Bronchitis Study Group

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References