MAJOR ARTICLE

Thrice-Weekly Clarithromycin-Containing Regimen for Treatment of *Mycobacterium kansasii* Lung Disease: Results of a Preliminary Study

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We initiated a prospective trial of an intermittent clarithromycin-containing regimen for the treatment of patients with *Mycobacterium kansasii* lung disease. Eighteen patients (10 men and 8 women) with *M. kansasii* lung disease received a regimen consisting of 500–1000 mg of clarithromycin, 25 mg/kg ethambutol, and 600 mg of rifampin 3 times per week. The primary treatment end point was a 12-month period during which sputum cultures were sterile while the patient was receiving therapy. Four male patients were lost to follow-up, but all of the remaining patients successfully completed therapy without significant drug-related adverse events. The mean time (± standard deviation [SD]) to sputum conversion was 1.0 ± 0.9 months, and the mean duration (± SD) of therapy was 13.4 ± 0.9 months. No patient who successfully completed therapy had relapsed after a mean (± SD) of 46 ± 8.0 months. Clarithromycin- and rifampin-containing regimens offer the possibility of effective short-course and intermittent treatment of *M. kansasii* lung disease.

Of all nontuberculous mycobacteria (NTM), *Mycobacterium kansasii* is considered to be the most virulent respiratory pathogen [1–5]. *M. kansasii* lung disease most closely parallels the clinical disease caused by *Mycobacterium tuberculosis,* including chest radiographic changes. Specifically, *M. kansasii* lung disease has traditionally been described as most frequently presenting with upper lobe cavitary infiltrates similar to those associated with pulmonary tuberculosis [1–5].

Untreated strains of *M. kansasii* are highly susceptible to the rifamycins; such strains have been found to have rifampin MICs ≤1.0 μg/mL [6–8]. The only drug for which resistance in vitro to a defined drug concentration has been regularly associated with failure of treatment of *M. kansasii* infection is rifampin [9, 10]. The current American Thoracic Society (ATS) recommendation for treatment of *M. kansasii* lung disease is an 18-month regimen that includes daily administration of isoniazid, rifampin, and ethambutol [10]. To date, no short-course or intermittent treatment regimen has been approved or endorsed by the ATS.

Clarithromycin also appears to be potent against *M. kansasii.* Untreated strains of *M. kansasii* are inhibited by clarithromycin at concentrations readily achievable in the serum with the standard therapeutic doses. Clarithromycin MICs for *M. kansasii* are typically 0.125–0.25 μg/mL, whereas clarithromycin MICs for *Mycobacterium avium* complex (MAC) are 1–4 μg/mL [7, 8]. It appears, in fact, that clarithromycin is sufficiently active to make use of short-course and/or intermittent therapeutic regimens for *M. kansasii* infection more feasible, when the agent is combined with rifampin. Significantly, preliminary studies of intermittent (3 times weekly) clarithromycin-containing regimens suggest that they are effective for treatment of MAC lung disease [11]. To date, to our knowledge, no studies have been published on the effectiveness of clarithromycin-containing or intermittent regimens for treatment of *M. kansasii* lung disease. We undertook a prospective,

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noncomparative trial of a controlled, intermittent clarithromycin-containing regimen for treatment of *M. kansasii* lung disease.

METHODS

Patients. Consecutive patients aged ⩾18 years who had *M. kansasii* lung disease and who had been referred to or received diagnoses at the University of Texas Health Center at Tyler (UTHCT) were considered for therapy and recruited to participate in the study. Details of these patients' clinical histories and potential disease risk factors were obtained. Diagnosis of *M. kansasii* lung disease was consistent with the most recent ATS diagnostic criteria for NTM lung disease [10]. Exclusion criteria included pregnancy, inadequate use of birth control, known allergy or intolerance to any of the study drugs, life-threatening illness, resistance of a pretreatment *M. kansasii* isolate to macrolides and/or rifampin, and identified risk factors or known positivity for HIV infection. Informed consent was obtained under a protocol approved by the Human Subjects Investigation Committee at UTHCT and by the US Food and Drug Administration under an investigational new drug application for clarithromycin.

Bacteriology. Sputum specimens were obtained daily for 3 consecutive days at enrollment in the study, in addition to at least 1 specimen every 4 weeks during therapy. Semiquantitative acid-fast bacilli (AFB) smears (fluorochrome method) were performed at a magnification of ×200, as described elsewhere [12]. Samples were cultured on Middlebrook 7H-11 agar and either Bactec 12B (Becton Dickinson) or ESP-MYC (Trek Diagnostics) broth. Cultures in which solid media were used were evaluated quantitatively, from no growth to 4+, by use of published standards, as described elsewhere [12]. Organisms were identified as *M. kansasii* with a commercial nucleic acid probe (AccuProbe; GenProbe).

A pretreatment *M. kansasii* isolate was tested for susceptibility to clarithromycin and rifampin. Broth microdilution with 2-fold drug dilutions using recently proposed NCCLS guidelines for susceptibility testing of *M. kansasii* was used [13]. The isolate was considered to be susceptible to macrolides if the clarithromycin MIC was ⩽16.0 μg/mL and susceptible to rifampin if the rifampin MIC was ⩽1.0 μg/mL [13].

Protocol. All patients received a rifampin- and clarithromycin-containing regimen 3 times per week (usually Monday, Wednesday, and Friday) that included clarithromycin (500 or 1000 mg/dose), rifampin (600 mg/dose), and ethambutol (25 mg/kg/dose). Two female patients who weighed <50 kg received 500-mg doses of clarithromycin; the other patients all received 1000-mg doses. For the first 6 months of participation, patients had follow-up appointments on a monthly basis, followed by every 2 months until completion of the study. Patients were dropped from the study if they missed consecutive scheduled appointments and did not respond to telephone and mail requests that the patient return.

Chest radiographs were obtained at entry to the study, approximately every 2–3 months during the study, and at discontinuation of the study medication. All chest radiographs were read by a staff radiologist at UTHCT and reviewed by one of the authors (D.E.G.).

Sputum conversion was defined as 3 consecutive sputum cultures negative for AFB, with the time of conversion considered to be the date of the first of the 3 negative sputum culture results. The therapeutic end point (i.e., treatment success) was a 12-month period during which all culture results were negative for AFB while the patient was receiving therapy.

Patients were questioned (with a standard questionnaire) about symptoms and problems (especially gastrointestinal) at baseline and at each clinic visit. In addition, a study coordinator was available 5 days per week by telephone. Laboratory safety tests consisted of baseline determination of the following values: liver enzyme levels (including of glutamyl transpeptidase and alkaline phosphatase), bilirubin levels, serum urea nitrogen levels, serum creatinine levels, and complete blood cell counts. The liver enzyme levels and complete blood cell counts were determined at monthly intervals for 6 months and then as needed thereafter. Visual acuity and red-green color discrimination (using Ishihara color plates) were tested at baseline, at monthly intervals, and whenever the patient complained of a change in vision.

Statistical analysis. Group values are expressed as mean ± SD.

RESULTS

Eighteen consecutive patients with *M. kansasii* lung disease were recruited during a 12-month period to participate in the treatment trial. All patients had sputum specimens that were smear positive for AFB and also had at least 3 cultures positive for *M. kansasii*. Details about these patients are provided in table 1.

The male patients were younger and more likely to be current cigarette smokers than were female patients. All 10 male patients and 3 female patients had bilateral upper lobe cavitary infiltrates typical of previously described *M. kansasii* lung disease (figure 1) [2]. Eight of the patients with cavitary disease, including the 3 women, had received a diagnosis of chronic obstructive lung disease before entering the study. Five female patients had nodular/bronchiectatic (i.e., noncavitary) lung disease, a pattern of disease that is well recognized in patients infected with MAC but has not been described elsewhere for *M. kansasii* lung disease (figure 2). Three of these patients had bilateral right middle lobe and lingular infiltrates, and 2 had disease confined to the right middle lobe. None of the patients

Table 1. Demographic and clinical characteristics of patients receiving an intermittent clarithromycin-containing regimen for treatment of *Mycobacterium kansasii* lung disease.

Characteristic	Male patients (n = 10)	Female patients (n = 8)	All patients (n = 18)
Age, mean years ± SD	50.2 ± 14.8	66.1 ± 11.1	58.5 ± 15.5
Current or former smoker	8	3	11 (61)
Noncavitary lung disease	0	5	5 (28)
Alcohol abuse	5	2	7 (39)
Previous therapy	5	3	8 (44)
Lost to follow-up	4	0	4 (22)
Completed therapy	6 (60)	8 (100)	14 (78)
Time to sputum conversion,[a] mean months ± SD	1.0 ± 1.0	1.0 ± 0.8	1.0 ± 0.9
Duration of therapy,[a] mean months ± SD	13.3 ± 0.8	13.4 ± 0.9	13.4 ± 0.9

NOTE. Data are no. or no. (%) of patients, unless otherwise indicated.

[a] Patients who were lost to follow-up (n = 4) were excluded from the analysis.

with noncavitary disease had an identified predisposition for bronchiectasis other than *M. kansasii* infection. Eight patients, 5 men and 3 women, all with cavitary disease, had received previous therapy with antituberculosis medications, including rifampin, isoniazid, and ethambutol. None of these patients had completed the 18-month course of therapy for *M. kansasii* disease recommended by the ATS [10].

Of the 18 patients, 4 male patients with cavitary lung disease were lost to follow-up a mean (±SD) of 4 ± 1.0 months (range, 3–5 months) after starting therapy. Three of these patients had experienced sputum conversion to AFB smear and culture negative before being lost to follow-up. The fourth patient did not send a sputum specimen for AFB analysis after the first month of therapy.

The remaining 14 patients, including 6 men and 8 women, all successfully completed therapy. These patients had conversion of sputum to AFB culture negative after a mean (±SD) of 1.0 ± 0.8 months (range, <1.0–4.0 months) and received a mean of 13.3 ± 0.8 months of therapy in total (range, 12–14 months). The patients who completed therapy did not receive any antimicrobial agents other than the study medications during their participation in the study. No patients experienced significant drug-related toxicity or required modification or discontinuation of the treatment regimen because of drug-related adverse events. All patients experienced symptomatic improvement while receiving therapy, including decreased cough and sputum production and improved fatigability. The mean weight gain (±SD) for patients who completed therapy was 5.6 ± 3.8 kg (range, 1–13.6 kg). All patients also experienced improvement in radiographic changes associated with *M. kansasii* infection. All pretreatment *M. kansasii* isolates were susceptible to clarithromycin and rifampin, and no isolate became resistant to either of these drugs while the patient was receiving therapy. Previous therapy did not appear to have an impact on response to therapy with the study medications. After a mean (±SD) of 46 ± 8.0 months, no patient who successfully completed therapy had experienced relapse.

DISCUSSION

A treatment regimen that included clarithromycin, rifampin, and ethambutol administered 3 times per week until the patient has had sputum cultures negative for AFB for a period of 12 months was effective in treating *M. kansasii* lung disease in 14 patients. This study also demonstrated that most patients who received the study regimen had prompt conversion of sputum to AFB culture negative (i.e., within 2 months), which is true of most patients who have drug-susceptible tuberculosis and are treated with standard antituberculosis therapy. Response to therapy in these patients did not appear to be adversely affected by previous treatment of *M. kansasii* infection, as long as the *M. kansasii* isolate remained susceptible in vitro to clarithromycin and rifampin.

Previous results of trials of short-course treatment (i.e., <18 months) of *M. kansasii* lung disease have provided some provocative results. The first trial of a short-course regimen was a study of 40 patients by Ahn et al. [14]; they found that the addition of 1 g of streptomycin twice weekly for the first 3 months to the previously recommended 3-drug regimen (isoniazid, rifampin, and ethambutol) administered for 12 months resulted in apparent cure of all but 1 patient. A second published trial, sponsored by the British Medical Research Council, of daily ethambutol (15 mg/kg) and rifampin (450–600 mg) administered for 9 months was completed and involved 154 patients. Sputum conversion was achieved in 99% of patients, but there was a relapse rate of 12% during a 5-year follow-up period [15]. A third study of a short-course regimen was published by Sauret et al. [16], who described 28 patients with *M. kansasii* lung disease. Fourteen patients received rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (25 mg/kg/

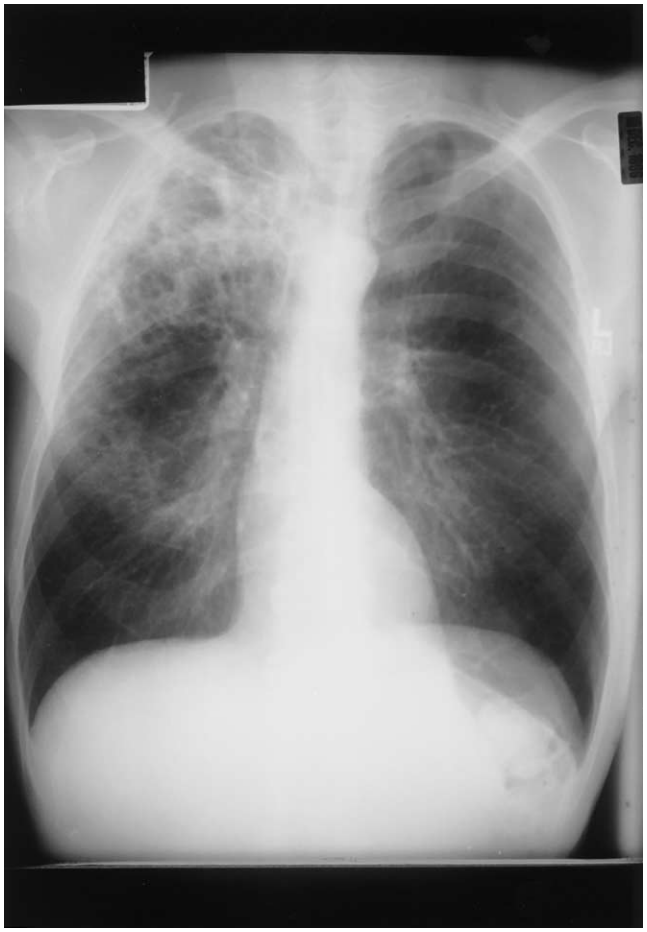

Figure 1. Radiograph for a 51-year-old male cigarette smoker with cavitary, predominantly upper lobe *Mycobacterium kansasii* lung disease.

day) daily for the first 6 months. Ethambutol was then discontinued, and administration of rifampin and isoniazid was continued for another 6 months. A second group of 14 patients were treated with the same regimen (including 6 months of ethambutol) for 18 months. All patients receiving both regimens had sputum conversion to negative for AFB. After 12–30 months of follow-up, only 1 patient (7%) in the 12-month treatment group and no patients in the 18-month group had experienced relapse after completing therapy.

The availability of a reliably effective short-course and/or intermittent treatment regimen for *M. kansasii* lung disease is extremely important; current recommendations (in the United States) suggest a total of 18 months of therapy [10]. Because there is no support for treatment of NTM diseases, including *M. kansasii,* from public health agencies, reduction of treatment costs is a high priority. A patient's inability to purchase medication, with attendant progression of disease, could lead to extensive lung destruction, debilitation, and death. Short-course, intermittent regimens also offer the potential for reducing drug toxicity and adverse events. Intermittent (3 times weekly) administration of ethambutol at, for example, 25 mg/kg/dose, appears to be associated with less ocular toxicity than does daily administration of ethambutol at 15 mg/kg/day for patients with MAC lung disease [17]. Conceivably, the prospect of fewer total doses over a shorter period of time might also improve patient compliance with treatment of *M. kansasii* lung disease. Treatment of this disease by directly observed therapy would also greatly benefit selected patients, but, again, there is no financial support from public health agencies for such an approach.

The availability of drugs, such as clarithromycin, that are highly active in vitro against *M. kansasii* for use in combination with rifampin, greatly enhances the prospects for developing effective intermittent and/or short-course regimens for treatment of *M. kansasii* lung disease. It is possible that administration of clarithromycin in just the first 2 months of therapy (in the "bactericidal" phase of treatment) might be a sufficient basis for a shorter duration of therapy. It has also become apparent that other newer agents, such as the newer 8-methoxy

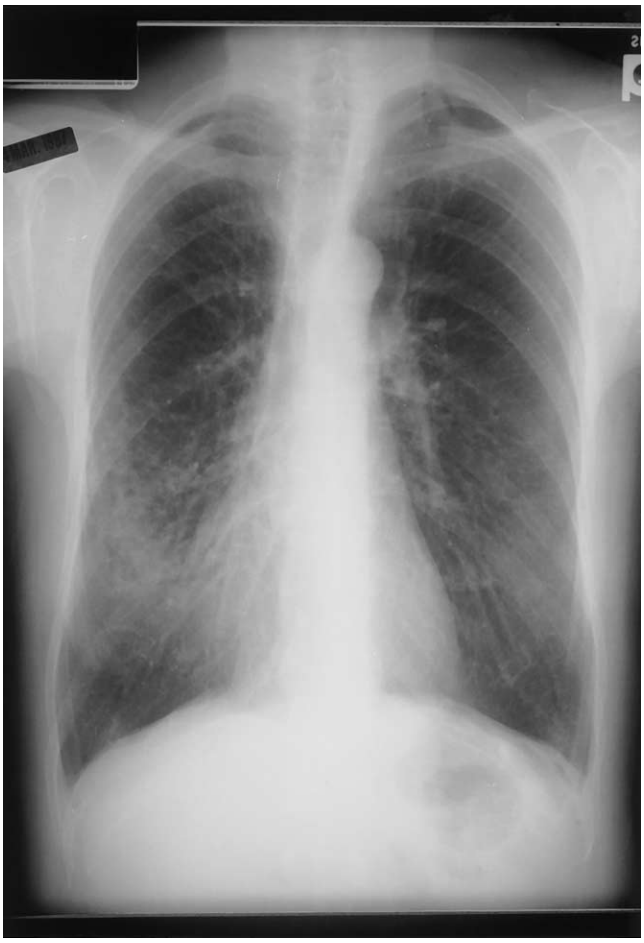

Figure 2. Radiograph for a 69-year-old nonsmoking female patient with predominantly mid-lung nodular/bronchiectatic *Mycobacterium kansasii* lung disease.

quinolones gatifloxacin and moxifloxacin and the oxazolidinone linezolid, also have excellent activity against *M. kansasii* [18, 19]. It is possible that a 6-month short-course regimen that includes clarithromycin, rifampin, and a newer quinolone or linezolid could be as effective as short-course regimens for tuberculosis.

There are problems with the present study, most notably the small number of patients treated. It would likely take a national cooperative study to recruit large numbers of patients, as has been done by the British Research Council. However, even though the number of patients involved is small, the results of this study suggest that rifampin and clarithromycin form the basis of a potent treatment regimen that can be effective when used on an intermittent basis. A second concern is the effect of rifampin on circulating clarithromycin levels, which did not appear to have a deleterious effect on outcome for our patients, who all had both rapid and sustained conversion of sputum to AFB smear and culture negative. The other major problem with this study is that even intermittent therapy with a clarithromycin-containing regimen for 13 months is very expensive. The estimated acquisition (wholesale) cost of 1000 mg of clarithromycin administered 3 times per week for 13 months at our institution is $1100. Finally, the length of follow-up is not yet sufficiently long to be absolutely certain that there will be no disease relapses.

This study also brought to light a previously unappreciated aspect of *M. kansasii* disease. Although nodular/bronchiectatic disease is the type present in up to 50% of patients with MAC lung disease [20], how often this form of lung disease occurs with *M. kansasii* is unknown. Patients with *M. kansasii* lung disease typically present with apical fibrocavitary abnormalities on chest radiographs. It is now apparent, and perhaps not surprising, that patients with *M. kansasii* lung disease can also present with noncavitary (nodular/bronchiectatic) infiltrates similar to those associated with MAC lung disease.

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