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Review Article

Treatment of pulmonary disease caused by *Mycobacterium kansasii*

Hung-Ling Huang [a,b,c,d], Po-Liang Lu [b,c,f], Chen-Hsiang Lee [g,h], Inn-Wen Chong [a,b,c,e,*]

[a] *Division of Pulmonary and Critical Care Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[b] *Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[c] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[d] *Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan*
[e] *Department of Respiratory Therapy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[f] *Department of Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[g] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan*
[h] *College of Medicine, Chang Gung University, Kaohsiung, Taiwan*

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As a cause of lung disease (LD), *Mycobacterium kansasii* is regarded as a highly virulent species among nontuberculous mycobacteria (NTM). Both the frequency of *M. kansasii* isolates and global prevalence of *M. kansasii*—LD have increased gradually over recent decades. Treatment of *M. kansasii*—LD is recommended because of the disease's poor prognosis and fatal outcome. The decision on the optimal time point for treatment initiation should be based on both the benefits and risks posed by multiple antimicrobial agents.

For treatment-naïve patients with *M. kansasii*—LD, rifampin-containing multiple antimicrobial regimens for ≥12 months after culture negative conversion are effective. However, some challenges remain, such as determining the precise length of treatment duration as well as addressing intolerable adverse effects, the uncertain effectiveness of isoniazid and ethambutol in treatment, the uncertain correlation between *in vitro* drug susceptibility testing and clinical outcomes, and the increasing prevalence of clarithromycin-resistant *M. kansasii* isolates. Short-course and effective therapies must be developed. New candidate drugs, such as tedizoid and clofazimine, exhibit excellent antimycobacterial activity against *M. kansasii in vitro*, but *in vivo* studies of their clinical applications are lacking.

This paper reviews the treatment, outcomes and future directions in patients with *M. kansasii*—LD.

* Corresponding author. Department of Internal Medicine, Kaohsiung Medical University Hospital, #100, Tzyou 1st Rd., Sanmin Dist., Kaohsiung, 80756, Taiwan. Fax: +886 7 3161210.
E-mail address: chong@kmu.edu.tw (I.-W. Chong).

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Introduction

Mycobacterium kansasii (*M. kansasii*) is one of the six most frequently isolated nontuberculous mycobacteria (NTM) species worldwide and is a common cause of opportunistic NTM infection associated with acquired immune deficiency syndrome (AIDS), second only to *Mycobacterium avium* complex (MAC).[1,2] Seven subtypes of *M. kansasii* have been identified; type I is the most common clinical pathogenic subtypes, with other types only recovered from environmental samples.[3]

M. kansasii is traditionally considered an NTM species with high virulence to cause lung disease (LD)[4], and *M. kansasii* isolation from sputum is always indicative of a true pathogen due to higher prevalence of NTM disease risk and features suggestive of active disease presented in patients with *M. kansasii* isolate even they didn't meet ATS case-definitions.[5,6]

The presentation of symptoms, histopathology, and images of patients with *M. kansasii*—LD resemble those in pulmonary tuberculosis.[7] Both the frequency of NTM isolation and global incidence of *M. kansasii*—LD have increased steadily in several regions, including south Africa, the United States, Poland, and Taiwan.[8,9] As indicated by updated hospital-based epidemiological data obtained in Taiwan, *M. kansasii* is the third most common NTM species causing pulmonary disease, with a 4.7-fold increase in the number of *M. kansasii* isolates between 2010 and 2014 and with an average incidence of 5.1 episodes per 100,000 hospital-based patient-years.[8] Clinicians must become more familiar with proper management of *M. kansasii*—LD as the global prevalence increasing.

Continuation of a rifampin containing regime that comprises at least 3 effective antimicrobial agents for at least 12 months after sputum culture negative conversion (SCC), which defined as 3 consecutive negative cultures after the first sputum sample collected at least 30 days apart, is recommended by the current American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guideline in 2007, and the British Thoracic Society (BTS) guideline in 2017.[9,10] Studies on this treatment regimen have reported favorable treatment response, noting a sustained sputum culture conversion (SSCC) rate without relapse of higher than 90%[5,10–13], but caution should be taken considering the lengthy and numerous adverse events (AEs) of multiple treatment regimens. AEs during treatment occurred in 14.7% of patients in one study, resulting in premature treatment failure or regimen modification.[14] The causative agents for intolerable AEs included streptomycin (6.3%), subsequently by isoniazid (4.0%), ethambutol (2.7%) and others (1.3%).[14]

The balance between the benefits and potential risks of AEs should be carefully evaluated before treatment initiation. Many challenges remain for clinicians needing to treat *M. kansasii*—LD. This review article focuses on the timing of treatment initiation, role of *in vitro* drug susceptibility testing (DST) in anti-*M. kansasii* treatment, and clinical outcomes of studies utilizing different antimycobacterial agents.

When anti-*M. kansasii* treatment should be initiated

The presence of at least two *M. kansasii* isolates from the respiratory tract, combined with clinical symptoms and typical radiographic characteristics, is essential for the diagnosis of pulmonary disease according to the current guidelines.[9,10] The clinical relevance of *M. kansasii* isolates from the respiratory tract was determined to vary from 12% to 83% based on the diagnosis criteria of the ATS/IDSA guideline, with the discrepancy due to the small heterogeneous sample recruited.[15–19] The largest multicenter retrospective study[20] conducted to date investigated the natural course of 109 patients with *M. kansasii*—LD to explore prognostic factors related to the disease. Two-thirds of the patients with *M. kansasii*-LD experienced radiographic progression within 1 year, and half of them died thereafter. The independent predictors for radiographic progression were high-grade sputum acid fast stain (AFS), fibrocavitary pattern, leucocytosis, old age, no other NTM species, and no concurrent diabetic mellitus. Thus, Initiation of antimycobacterial therapy is considered for above high-risk populations with the aforementioned predictors of radiographic progression.

Some experts have stated that the diagnostic threshold should be adjusted according to the patient's immune status. A single *M. kansasii* isolate from expectorated sputum may be clinically relevant in people living with human immunodeficiency virus (HIV)[6,15] or cavitary LDs.[5,21] A retrospective, longitudinal, multicenter study[22] conducted on a non-HIV population reported that *M. kansasii*—LD developed within 1 year in 16 of its 83 patients (19%) with single *M. kansasii* isolate from $\geq$3 expectorated sputum samples, and the independent risk factors included high-grade sputum AFS at initial presentation, prior elementary occupation, and high initial radiographic score ($>$6).[23] Initiation of antimycobacterial therapy is recommended for these high-risk populations because of the disease's potentially fatal outcome; the mortality rate was noted at 44% for cases after *M. kansasii*—LD developed.[22]

Aggressive antimycobacterial treatment is recommended for patients with advanced HIV disease and AIDS as well as *M. kansasii*—LD. The mortality rate can exceed 50% if the disease is left untreated.[24] The factors that predicted mortality in this specific population were low CD4 cell count, lack of highly active antiretroviral therapy, positive

sputum AFS, and lack of adequate mycobacterial treatment.[25]

Clinical relevance of *in vitro* DST in *M. kansasii*—LD treatment

In vitro susceptibility testing of *M. kansasii* to each antimycobacterial agent was interpreted in the guidelines from the Clinical and Laboratory Standards Institute (CLSI).[26] Minimum inhibitory concentrations (MICs) were determined using serial twofold dilutions, and MIC_{50} and MIC_{90} were defined as the lowest concentration able to inhibit 50% and 90% of isolates *in vitro*, respectively.[26,27]

Since 1971, rifampin has been regarded as the crucial component of multidrug regimens for *successfully* treating *M. kansasii.12 One* study analyzed multiple mycobacterial drug susceptibility in *M. kansasii* strains from patients with *M. kansasii*—LD who were experiencing relapse or treatment failure; the rifampin-resistant strain (MICs >1.0 μg/mL) was associated with treatment failure.[28] Because rifampin significantly enhances their metabolism, rifampin should be avoided for patients with concurrent HIV who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Rifabutin (MICs ≤ 2.0 μg/mL) is used instead of rifampin to prevent acceleration of hepatic metabolism.[29]

Acquired resistance of rifampin was discovered to occur in approximately 4% of *M. kansasii* isolates, caused by suboptimal therapy and HIV coinfection.[30,31] Phenotypic rifampin resistance in *M. kansasii* isolates is highly associated with multiple missense mutations in a short segment of the RNA polymerase gene, as is that in *Mycobacterium tuberculosis*.[3,32]

According to the previous study, macrolide exhibits favorable outcome *in vitro* activity against *M. kansasii isolates, indicating its importance in the treatment of M. kansasii—LD*.[33] However, the wide use of macrolides as the first-choice treatment for respiratory infection has contributed to the increased prevalence of clarithromycin-resistant (MICs ≥ 0.25 μg/mL) *M. kansasii* strains, with this prevalence varying from 0% to 20.5% across different countries.[33–36] Efflux pumps and the methylation of 23S rRNA may be involved in the clarithromycin resistance of *M. kansasii*.[29] In addition, a study analyzing 78 *M. kansasii* isolates from patients in 16 provinces of China demonstrated that the predominant *M. kansasii* subtype 1 was associated with clarithromycin resistance, and that the presence of mutations in 23S rRNA was associated with 56.2% of clarithromycin-resistant *M. kansasii* isolates.[34]

The current method for interpretation of MIC for isoniazid against *M. kansasii* utilizes the critical concentrations (0.2 μg/mL, 1 μg/mL) in Middlebrook 7H10 agar for *M. tuberculosis* susceptibility testing. However, the MICs for isoniazid against untreated strains of *M. kansasii* ranged from 0.5 to 5.0 μg/mL, which will cause a false interpretation in isoniazid resistance.[29,31] Therefore, the drug susceptibility to isoniazid is not routinely recommended.[26,27]

The MIC results of ethambutol are not reproducible by broth microdilution, which might contribute to be misleading from effective regimen for *M. kansasii* treatment[26], but it was found to inhibit the emergence of rifampin-resistant organisms.[37]

Pyrazinamide is unacceptable as an alternative drug for treating *M. kansasii* infection because of the bacterium's high pyrazinamide resistance *in vitro*.[3,27,29]

M. kansasii is more susceptible *in vitro* to the newer 8-methoxy quinolones gatifloxacin and moxifloxacin than to ciprofloxacin and levofloxacin. However, increased *in vitro* resistance to ciprofloxacin and moxifloxacin (30% and 40%, respectively) due to the widespread use of quinolones in high TB endemic area, will constitute a potential threat to treating *M. kansasii*—LD.[38,39]

Although *M. kansasii* is susceptible *in vitro* to numerous drugs, information is limited on clinical usefulness, and their correlations with clinical outcome remains uncertain. Therefore, the current guideline only highlights the importance of *in vitro* rifampin and clarithromycin susceptibility testing of an isolate prior to the initiation of treatment and subsequent reculture of *M. kansasii* isolates when treatment failure occurs.[9,10]

Treatment of rifampin-susceptible isolates

Untreated strains of *M. kansasii* are highly susceptible to rifampin (MICs ≤ 1.0 μg/mL). For these strains, combination multidrug rifampin-based therapy is recommended to prevent the development of rifampin resistance for which even companion drugs may not enhance their efficacy.[28,40] The conventional first-line treatment is the combination of rifampicin with maximum 600 mg daily for adults >50 kg or 450 mg daily for patients <50 kg, 15 mg/kg of ethambutol daily, and 300 mg of isoniazid daily or a regimen in which isoniazid is replaced by another drug, such as 250—500 mg of azithromycin or 1,000 mg of clarithromycin daily.[9,10] The current recommendations for *M. kansasii*—LD treatment are mostly based on observational data and understanding of *in vitro* susceptibility, because no randomized comparative trials have yet evaluated the treatment efficacy of different combinations.

The role of isoniazid in treating patients with *M. kansasii*—LD was evaluated by a large prospective study conducted by the BTS.[11] Standard isoniazid-containing antituberculosis regimens [HERZ (combination of ethambutol, isoniazid, rifampin, and pyrazinamide) or SHRZ (combination of streptomycin, isoniazid, rifampin, and pyrazinamide)] were administrated to 149 patients among 173 patients with NTM-LD prior to species identification, and the regimen was then changed to ethambutol and rifampin alone for an additional 9 months once *M. kansasii* had been identified. The remaining 24 patients received only ethambutol and rifampin for 9 months. Pretreatment bacteriological analysis revealed that all isolates were resistant to isoniazid and pyrazinamide, but none were resistant to rifampicin or ethambutol. SCC was achieved in 99% of patients. No significant difference was discovered in the relapse rate of those using isoniazid-containing versus non-isoniazid-containing regimens (8.7% vs. 8.3%) at a median of 23 months following treatment cessation. Relapse was mostly attributed to medication noncompliance or severe underlying disease. We reasonably speculated that isoniazid might be an unnecessary part of the combination regimen for *M. kansasii*—LD treatment owing to the fact that 100% of the isolates were resistant to isoniazid, and

concluded that 9 months may not be a sufficiently long treatment period.

The treatment value of isoniazid in the currently recommended regimen is questionable, and some experts have replaced isoniazid with macrolide to more effectively treat *M. kansasii*—LD.[41–43] A prospective study demonstrated that an intermittent clarithromycin- and rifampin-containing regimen (500—1,000 mg of clarithromycin, 25 mg/kg of ethambutol, and 600 mg of rifampin thrice weekly) was effective for patients with *M. kansasii*—LD. A total of 18 patients received treatment for an average duration of 13.5 months, and the mean time to SCC was 1 month, with no relapses occurring during a mean follow-up of 46 months.[41] Another retrospective study recruited 56 patients with *M. kansasii*—LD; all patients were treated with daily rifampicin (600 mg), ethambutol (25 mg/kg for the first 2 months, and then 15 mg/kg), and clarithromycin (1,000 mg daily) for a mean duration of 21 months regardless of DST results. The mean time to SCC was 8.9 months after treatment, and all patients were cured without mention of the follow-up relapse rate.[42]

A retrospective study concluded the treatment effect is similar between macrolide-containing regimen (n = 25, including 19 received daily treatment and 6 received three-times-weekly intermittent treatment) and an isoniazid-containing regimen (n = 24) by analyzing 49 patients with *M. kansasii*-LD directly. The time to SCC (median 2.0 months vs. 1.2 months; p = 0.838) were similar between isoniazid group and macrolide group after follow-up. Only 1 patient in isoniazid group experienced recurrent *M. kansasii*-LD at the median follow-up duration of 13.5 months.[43] Clarithromycin-containing regimens without isoniazid are likely to effectively treat *M. kansasii*—LD. A further comprehensive and large-scale prospective study should be conducted to optimize the protocol.

Treatment of rifampin-resistant isolates

Failure of treatment for *M. kansasii*—LD is unusual and always associated with rifampin or clarithromycin resistance.[31,32] Once rifampin resistance has been detected, a regimen consisting of at least three drugs should be selected on the basis of, but not dictated by, the results of DST for other potential drugs.[9]

The CLSI guidelines recommend additional tests for isoniazid, ethambutol, amikacin, streptomycin, ciprofloxacin, moxifloxacin, clarithromycin, rifabutin, and cotrimoxazole.[27] *M. kansasii* has excellent *in vitro* susceptibility to regimens containing these drugs, and these regimens are thus likely to be effective in treating *M. kansasii*—LD[44], although the results should be interpreted with caution because of the lack of data on the correlation of *in vitro* activity with such regimens and *in vivo* efficacy.

Resistance to isoniazid and ethambutol may occur together with rifampin resistance in *M. kansasii* isolates, but the mechanism remains uncertain. An *in vitro* study demonstrated that the synergistic interactions between drugs resulted in higher susceptibility of clinical isolates toward combinations of ethambutol and other anti-*M. kansasii* agents, including rifampin, isoniazid, and ciprofloxacin.[37,41] Some studies have reported resistances of *M. kansasii* isolates to ethambutol ranging from 0% to 97.9%, and this large range was due to the different methods used to determine susceptibility.[3,28,40] Studies have yet to investigate the clinical relevance of isoniazid and ethambutol resistance in treatment of *M. kansasii*—LD.

A combination of oral and injectable agents has been demonstrated to be effective in patients with a rifampin-resistant strain of *M. kansasii*—LD.[28,31] In a retrospective study of eight patients with cavitary disease caused by rifampin-resistant *M. kansasii* for whom treatment had failed, researchers used a combination of intermittent parenteral streptomycin or amikacin (included only for the initial 2—4 months) with high-daily-dose isoniazid (900 mg), high-dose ethambutol (25 mg/kg daily), and sulfamethoxazole (1.0 g thrice daily). SCC occurred in a mean of 10 weeks, and no follow-up results were reported.[28]

Another retrospective study[31] of 36 patients with rifampin-resistant *M. kansasii*—LD, including 10 patients who were seropositive for HIV, demonstrated that the combination of high-dose isoniazid (900 mg/day), ethambutol (25 mg/kg daily), trimethoprim/sulfamethoxaole (1 g thrice daily), and either amikacin (500 mg) or streptomycin (500—1,000 mg) five times weekly for 1—3 months may be an effective option; this regimen resulted in a high percentage (90%) of initial SCC within a mean of 11 weeks. However, bacteriologic relapse occurred in four out of five patients (80%) who withdrew from therapy less than 6 months after culture negative conversion, and the relapse rate decreased to 8.3% for patients who had received at least 12 months (mean: 16.3 months) of therapy. The study suggested that multiantimicrobial therapy with a sufficient treatment duration is effective even for patients with HIV.

Treatment duration for *M. kansasii*—LD

The duration of treatment for *M. kansasii*—LD is determined by either the cure rate or relapse rate. Serial sputum bacteriology surveillance and periodic chest radiographs are indicative of a medication's efficacy. SSCC is the primary indicator of a patient being cured, and the time to sputum conversion may help determine the length of therapy. For patients with pulmonary infection caused by rifampin-susceptible *M. kansasii*, the cure rate is excellent at up to 99% when a rifampin-containing regimen is used.[11,12,45,46] The relapse rate appears to be associated with treatment duration. A prospective study analyzing 28 patients with *M. kansasii*—LD reported a higher relapse rate in those receiving 12 months of HER (combination of isoniazid, ethambutol and rifampin) than in those receiving 18 months of HER (3.5% vs. 0%).[46]

Two studies aimed to evaluate whether the combination of parenteral streptomycin during the first 2—3 months with a rifampin-based regimen could shorten the treatment course to 12 months.[12,14] A prospective study reported that 1 of 40 patients (2.5%) relapsed 6 months after completing chemotherapy during the average follow-up of 31 months.[12] Another retrospective study of

75 patients with *M. kansasii*—LD reported a cure rate of 82.8% and relapse rate of 2.19 per 100 person-years after a 41.5-month median follow-up.[14] These findings imply that a 12-month fixed-course treatment, even when adding parental antimicrobial agents, may still not be long enough to cure all patients with *M. kansasii*—LD. Therefore, the current guidelines recommend that long-lasting therapy with multiple antimicrobial regimens for at least 12 months after SCC is necessary to lower the relapse rate.[9,10]

Current evidence supports the treatment duration for *M. kansasii*—LD in patients with HIV coinfection could be comparable with that of immunocompetent patients. However, treatment prolongation to at least 6—12 months after immune restoration should be considered for patients with blood culture isolates.[10]

Potential regimens for treating *M. kansasii*—LD

To shorten the course and increase the effectiveness of treatment, several new agents—such as oxazolidinones (linezolid, tediozlid, contezolid, and sutezoid), riminophenazines (clofazimine), nitroimidazoles (delamanid), diarylquinoline (bedaquiline), glycylcyclines (tigecycline), and nitroimidazopyran (pretomanid)—are candidates.[47] However, clinical data indicating when one alternative regimen should be used rather than another are extremely limited, and relatively few appropriate animal models have been employed to mimic *M. kansasii* pulmonary infection.[48]

Oxazolidinones were found to be active *in vitro* against the multidrug-resistant *M. tuberculosis* strain and were also determined to have favorable *in vitro* activity with excellent MIC_{50} and MIC_{90} against *M. kansasii*.[49] Among the oxazolidinones, sutezolid has been identified as the most active antimicrobial agent in terms of MIC_{50} and MIC_{90} (at 0.125 and 0.25 μg/mL, respectively) relative to tedizolid (at 0.5 and 0.5 μg/mL, respectively) and linezolid (at 1 and 2 μg/mL, respectively).[44,47,49] Linezoid, the first US Food and Drug Administration—approved oxazolidinone, has been effective in the treatment of patients with multidrug-resistant tuberculosis infection, but its potential toxicity limits its long-term utility.[50] Although Tedizolid's safety profile is superior to linezolid's,[51] Tedizolid has not been adequately studied in relation to *M. kansasii* infections.

Long-duration clofazimine-containing regimens have been demonstrated as being safe, well tolerated, and able to improve treatment outcomes in patients with MAC and *Mycobacterium abscessus*—LD.[52—54] One study noted that 90% of *M. kansasii* isolates had a clofazimine MIC_{90} $\leq$0.5 mg/L.[55]

In addition, the low MICs of delamanid and bedaquiline against clarithromycin-resistant *M. kansasii* strains imply the potential antimycobacterial effects of these drugs *in vivo*.[56]

However, clinical studies in which these novel regimens are applied to patients with *M. kansasii*—LD remain lacking.

AEs of anti-*M. kansasii*—LD treatment

Multiple antimicrobial agents should be used for long periods with caution due to potential drug-related AEs. Drug intolerances and adverse drug—drug interaction will hinder successful treatment completion. Few studies have raised safety concerns toward such treatments of *M. kansasii*—LD, and the proportion of AEs during treatment has varied from 0% to 14.7%.[14,41,46] This inconsistency was due to small sample sizes, different study designs, inconsistent regimens and follow-up protocols. Specific drug toxicities and monitoring recommendations have been outlined in detail[57], and we introduce them briefly here.

Rifampin is a strong inducer for the hepatic cytochrome enzyme system, which may interfere with the metabolism of concurrent medication. AEs include dyspepsia, nausea, vomiting, diarrhea, headache, fever, rash, itchiness, hepatotoxicity, leukopenia, and a flu-like syndrome.[58] Ethambutol may cause visual acuity, red—green color discrimination, and optic neuropathy in approximately 5% of patients when it is used at daily doses greater than 15 mg/kg.[59] The major AEs of aminoglycoside include vestibular and auditory toxicity and renal dysfunction.[60] Sensorineural hearing loss can occur with macrolide use.[61] The notable AEs of linezoid were reported to be peripheral neuropathy, gastrointestinal intolerance, anemia, and thrombocytopenia.[62] Prolongation of the QTc leads to dysrhythmia when macrolides, fluoroquinolones, clofazimine, and bedaquilline are used[61,63,64], and caution is thus advised along with the use of electrocardiogram monitoring.

Regular clinical and laboratory monitoring during antimicrobial drug therapy can optimize patient tolerance and ensure a high completion rate. To evaluate possible drug toxicity, follow-up protocols should be established and tailored to the individual.

Future research directions

M. kansasii—LD is regarded a treatable disease and has favorable prognosis if treated appropriately. Management of *M. kansasii*—LD requires the efforts of interdisciplinary experts, and clinicians must know how to properly manage *M. kansasii*—LD because of the increasing prevalence of this disease.

However, several obstacles for treating *M. kansasii*—LD remain. First, *M. kansasii* isolates differ greatly by geography, and a formal large-scale public health study should be conducted to determine the exact prevalence of *M. kansasii*—LD. Second, because of the frequent use of antibiotics in treating different infectious diseases, drug-resistant *M. kansasii* isolates may become more prevalent. Third, standard methods of subtype identification are lacking. Fourth, DST is not routinely performed in many areas. Fifth, the lack of an *in vivo* animal model to optimize the appropriate protocol will interfere with the application of new regimens in clinical trials.

Appropriate animal models should be developed to evaluate the effectiveness and safety of different combinations of traditional drugs and recently licensed or new experimental compounds in treating *M. kansasii*—LD.

A local expert consortium should be established to integrate clinical resources and launch multicenter studies with the objective of optimizing new regimens and establishing a standard follow-up protocol for *M. kansasii*—LD treatment.

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Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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