Short-course chemotherapy for mycobacteriosis kansasii?

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The success of short-course chemotherapy for tuberculosis, the similarity between *Mycobacterium tuberculosis* and *M. kansasii* and the effectiveness of rifampin against the latter organism prompted a comparison of the diseases due to these organisms to assess the feasibility of a prospective trial of short-course chemotherapy in patients with mycobacteriosis kansasii. The two groups of patients were matched for age, sex and time of diagnosis. The patients with mycobacteriosis kansasii more frequently had underlying obstructive pulmonary disease. The clinical course of mycobacteriosis kansasii was more indolent, with a slower rate of improvement according to the chest x-ray films and a longer time before sputum smears and cultures became negative. *M. kansasii* was significantly more resistant to all the antibiotics, including rifampin. Although these differences from tuberculosis suggest that an equally short course of therapy may not be effective for patients with mycobacteriosis kansasii, the outcome was good in compliant patients who were given the three most effective major drugs for 12 months after the sputum smears and cultures had become negative. Therefore, a trial of modified short-course chemotherapy is recommended for patients with mycobacteriosis kansasii.

Le succès de la chimiothérapie en traitement court contre la tuberculose, la similitude de *Mycobacterium tuberculosis* et *M. kansasii* et l'efficacité de la rifampicine contre ce dernier organisme ont incité les auteurs à comparer les maladies dues à ces deux organismes afin d'établir la possibilité de conduire une étude prospective de la chimiothérapie en traitement court dans les infections à *M. kansasii*. Deux groupes de patients furent appariés pour l'âge, le sexe et le moment du diagnostic. Les patients infectés par *M. kansasii* étaient plus souvent porteurs d'une maladie pulmonaire obstructive sous-jacente. L'évolution clinique de l'infection à *M. kansasii* était plus torpide, montrant à la radiographie pulmonaire un taux d'amélioration plus lent et nécessitant un temps plus long avant que les frottis et les cultures de crachats deviennent négatifs. *M. kansasii* était beaucoup plus résistant à tous les antibiotiques y compris la rifampicine. Bien que ces distinctions par rapport à la tuberculose laissent supposer qu'un traitement court puisse ne pas être efficace chez les patients infectés par *M. kansasii*, les résultats ont été bons chez les patients fidèles au traitement qui ont reçu les trois médicaments les plus efficaces pendant 12 mois après que les frottis et les cultures de crachats furent devenus négatifs. Il est en conséquence recommandé de procéder à une étude d'un traitement court modifié de chimiothérapie chez les patients infectés par *M. kansasii*.

Mycobacterium kansasii is a nontuberculous, photochromogenic mycobacterium. Unlike other atypical mycobacteria the presence of organisms usually signifies disease. Most patients with disease due to *M. kansasii* present with systemic symptoms, such as hemoptysis or weight loss, radiologic evidence of cavitary lesions of the lungs and acid-fast bacilli in their sputum. Patients are usually treated with antituberculous agents.

The pathological features of the diseases caused by *M. kansasii* and *M. tuberculosis* are similar, and *M. kansasii* is biochemically, enzymatically and antigenically the mycobacterium most closely related to the tubercle complex,[1] although it used to be characterized by its resistance to the commonly used antimycobacterial drugs.

Before the use of rifampin, the treatment of mycobacteriosis kansasii was difficult, and the success rate was so different from that for tuberculosis that further comparison of the diseases has seldom been considered. However, rifampin, which has been the cornerstone of short-course chemotherapy for tuberculosis, has been reported to be very effective against mycobacteriosis kansasii:[2-5] "Recent reports of regimens containing rifampin have demonstrated success rates rivalling the results with tuberculosis therapy."[6] However, whereas short-course chemotherapy has been very successful for tuberculosis,[7] its use has so far not been reported for mycobacteriosis kansasii. A comparison of these diseases, with attention to the possibility of short-course chemotherapy, therefore seemed timely.

Can a treatment regimen similar to that used for tuberculosis be used in patients with mycobacteriosis kansasii? The definitive answer requires a prospective trial, but a retrospective study comparing patients with disease due to *M. kansasii* and those with tuberculosis could determine the value of such a trial. We first sought to examine the appropriateness of tuberculosis as a model; that is, are patients with mycobacteriosis kansasii similar to those with tuberculosis, are the organisms similar, is the clinical course similar, and how do the final outcomes of the two diseases compare?

There have been only a few studies that have compared the diseases caused by these mycobacteria,[8]

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and none in which the patients were matched by year of diagnosis, age and sex. We used pair matching to set up the control group (patients with tuberculosis). We matched the groups by age and sex because of the effects of these factors on the various outcomes, including death, and by year of diagnosis to ensure that a similar overall therapeutic approach was used at the time of diagnosis, particularly because we included patients over an extended period. Separate comparisons with respect to the use of rifampin were used to determine whether the use of this drug had lessened the morbidity and mortality in patients with mycobacteriosis kansasii as much as it had in those with tuberculosis.

Patients and methods

The clinical records of all the patients for whom more than one culture of *M. kansasii* was grown and who had been treated at the Montreal Chest Hospital Centre between 1962 and 1980 were reviewed. For all patients we tabulated age, sex, occupation, residence, country of birth and medical history (which included whether they had been vaccinated with bacille Calmette–Guérin [BCG], their smoking habits and their history of exposure to tuberculosis), symptoms and signs of illness, skin test results, radiologic findings, length of hospital stay, adverse reactions and duration of treatment with each drug. The variables used in the analysis of outcome were death, residual impairment, recurrence of disease, amount of time away from work (when applicable), and duration of radiologic abnormality and of smear and culture positivity of the sputum.

The drug susceptibility of the infecting organisms was recorded for each patient. The colony growth on media containing three dilutions of antibiotics was expressed as a percentage of the control colony growth. Susceptibility was scored as follows: 0, no growth at any dilution; 1, 25% or less growth at mid-dilution; 2, 26% to 100% growth at mid-dilution; 3, 100% growth at mid-dilution and growth at the highest concentration of antibiotic.

To be included in the study, the patients with mycobacteriosis kansasii had to have had multiple cultures showing a substantial number of colonies and either new, systemic symptoms or radiologic changes. Since there were no cases of nonpulmonary disease due to *M. kansasii*, matching was done only with patients who had pulmonary tuberculosis, first by sex and then by age, to a maximum variation of 3 years, and by year of diagnosis to a maximum variation of 2 years. If more than one control patient met the criteria for the matching, one was selected at random for the comparison.

Most of the patients in both groups had been inpatients in the tuberculosis unit of the Montreal Chest Hospital Centre, which had used rifampin since 1973 and unsupervised (i.e., following discharge from hospital the patients were responsible for their treatment) short-course therapy since 1976. Owing to the director's interest in atypical mycobacteria, the hospital's laboratory received specimens from 33 Quebec hospitals. Most of the patients had been followed up for several years after quiescence of the disease.

After 1976 the initial therapy for both groups was rifampin, 600 mg per day, ethambutol, 15 mg/kg per day, and isoniazid, 300 mg per day. When the results of culture and sensitivity testing became available, after 8 weeks, the therapy was changed. For illness due to *M. tuberculosis* sensitive to rifampin and isoniazid, ethambutol was discontinued, and the other two drugs were given daily for 9 months. If the sputum cultures continued to be positive for more than 3 months, this treatment was continued for 1 year. If the causative organism was identified as *M. kansasii*, the therapy was changed to whichever three of the five major drugs (isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide) were most effective in vitro. Therapy was continued for 9 to 12 months after the organisms could no longer be isolated from the sputum. In both groups of patients, whenever the organisms were thought to be drug-resistant or when the patient was thought likely to be noncompliant or was extremely ill, streptomycin and pyrazinamide were added to the initial regimen to reduce the mycobacterial load as rapidly as possible.

Treatment regimens used before 1976 did not include rifampin, and the total duration of therapy for tuberculosis had been 2 years. For disease due to *M. kansasii*, therapy with the three most effective drugs had been continued for 2 years after the sputum cultures became negative.

This was not a truly paired experiment, in which the groups are alike in all respects except the characteristic under consideration, similar treatment is given and the groups are followed forward. It is, therefore, controversial whether paired or unpaired analysis should be performed.[9-13] We compared the population characteristics, antibiotic resistance patterns and clinical variables in an unpaired manner with the use of contingency tables without correction for continuity,[14] Fisher's exact test and the *t*-test.[15] We also used the paired *t*-test and McNemar contingency table analysis.[16] However, since there was no significant difference between the two methods, we report only the results of the unpaired analysis.

To compare the results of therapy, we considered only the patients who had completed their treatment regimen without interruption and who had either received rifampin initially or had not received it at all.

Results

A total of 36 patients with mycobacteriosis kansasii met the criteria for our study (Table I). For none of these patients did culture show concurrent growth of more than one species of mycobacteria. The average age in both groups was 53 years, but more of the patients with tuberculosis were retired ($p = 0.05$). Of the 36 patients, 94% were male. Although there was no difference in place of birth or occupation between the groups, the proportion of patients with mycobacteriosis kansasii who lived in the city was less than that for the patients with tuberculosis. Nine (25%) of the patients with mycobacteriosis kansasii and 18 (50%) of those with tuberculosis were judged by their physicians to abuse alcohol. About half of those with mycobacteriosis kansasii, compared with only 8% of those with tuberculosis, had obstructive pulmonary disease. However, smoking

was more frequent and heavier among the patients with mycobacteriosis kansasii. Only one patient with mycobacteriosis kansasii had anthrosilicosis.

Each symptom and sign except hemoptysis was more frequent in the patients with tuberculosis, but the frequency of any symptom and the average number of symptoms per patient were not significantly different (Table II).

Table I—Characteristics of 36 patients with mycobacteriosis kansasii and 36 with tuberculosis,* matched for age and sex

Characteristic	Patients with mycobacteriosis kansasii	Patients with tuberculosis	p value†
Mean age (yr)‡	53.3 (0.4)	53.1 (0.4)	–
Sex (male:female ratio)	34:2	34:2	–
Residence (urban:rural ratio)	26:9	33:3	0.05
Country of birth (Canada:non-Canada ratio)	28:8	27:8	NS
Associated conditions (no. of patients)			
Remote tuberculosis	8	12	NS
Alcohol abuse	9	18	0.03
Obstructive pulmonary disease	17	3	0.0002
Emphysema	3	1	NS
Bronchitis	1	0	NS
Bronchiectasis	2	0	NS
Mixed chronic	11	2	0.006
Lung cancer	4	2	NS
History of gastrectomy	3	3	NS
Cigarette smoking			
No. of patients who smoked	31	26	NS
Mean amount smoked (pack years)‡	40 (4.8)	27 (3.7)	0.05

*Patients were excluded from the analyses in Tables I through IV if the information was ambiguous or not available.
†NS = not significant.
‡Numbers in parenthesis are standard errors of the mean (SEM).

Table II—Selected symptoms and signs at time of presentation

Symptoms and signs	No. (and %) of patients with: Mycobacteriosis kansasii*	Tuberculosis
Symptoms		
New cough	15 (42)	23 (64)
New sputum production	14 (39)	18 (50)
Chest pain	5 (14)	9 (25)
Weakness	14 (39)	16 (44)
Anorexia	7 (20)	12 (33)
Hemoptysis†	12 (33)	5 (14)
Fever	12 (33)	11 (30)
Weight loss	18 (50)	24 (67)
Mean no. of symptoms per patient and (SEM)	2.7 (0.05)	3.3 (0.05)
Signs		
Cachexia	1 (3)	3 (8)
Hepatomegaly†	1 (3)	6 (17)
Liver function abnormality	2 (6)	6 (17)
Positive results of smear	24 (67)	27 (75)

*Two patients had no symptoms.
†The frequency in the two groups was significantly different at p = 0.05.

The type, extent and location of changes on the chest x-ray films also did not differ significantly between the two groups (Table III). However, most (80%) of the patients with mycobacteriosis kansasii had cavitary disease.

Most of the isolates of *M. tuberculosis* were sensitive to all the drugs tested, whereas most of those of *M. kansasii* were at least partially resistant to most of the antibiotics (Fig. 1). In vitro, rifampin was clearly the most effective drug against *M. kansasii*, but ethambutol, pyrazinamide, streptomycin, ethionamide and isoniazid frequently showed some activity and were used even though some resistance was present. Para-aminosalicylic acid was the least effective agent.

The outcome of treatment, as measured by whether the patient died, had residual impairment or a recurrence of disease, or returned to work, was good in both groups (Table IV). Most deaths occurred after the therapy had been completed and were attributed to other disease. The average duration of follow-up was 4.3 years in the patients with mycobacteriosis kansasii and 2.7 years in those with tuberculosis. Adverse effects of

Table III—Changes on chest x-ray films*

Changes and their location	No. (and %) of patients with: Mycobacteriosis kansasii	Tuberculosis
Changes		
None	4 (11)	1 (3)
Cavities	29 (80)	23 (64)
"Chronic" pleural changes	17 (47)	18 (50)
Pleural fluid	3 (8)	8 (22)
Other "chronic" abnormalities	29 (80)	26 (72)
Zone of changes		
Right upper	26 (72)	27 (75)
Right middle	7 (19)	13 (36)
Right lower	7 (19)	14 (39)
Left upper	21 (58)	23 (64)
Left middle	8 (22)	9 (25)
Left lower	8 (22)	15 (42)

*No difference between the two groups was significant.

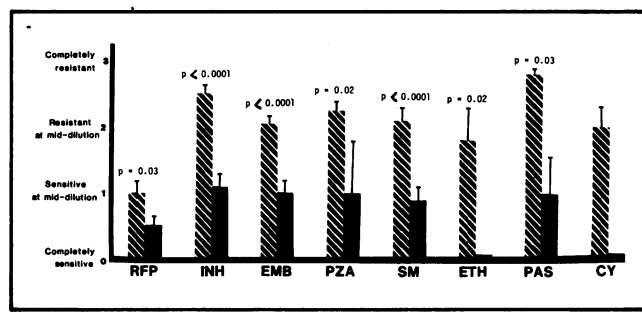

FIG. 1—Mean score for in-vitro resistance (± standard error of the mean) of isolates of *Mycobacterium kansasii* (broken bars) and *M. tuberculosis* (solid bars) to rifampin (RFP) (in 25 and 19 patients respectively), isoniazid (INH) (in 36 and 30 patients), ethambutol (EMB) (in 27 and 21 patients), pyrazinamide (PZA) (in 16 and 4 patients), streptomycin (SM) (in 32 and 30 patients), ethionamide (ETH) (in 5 and 21 patients), para-aminosalicylic acid (PAS) (in 24 and 5 patients) and cycloserine (CY) (in 10 and 0 patients).

medication were rare except with cycloserine. Only a few patients had residual impairment that could be attributed to mycobacterial disease, and only one patient in each group had a recurrence of disease. More patients with mycobacteriosis kansasii returned to work after recovery.

Although the smears and cultures of sputum remained positive longer and the time to the first radiologic evidence of improvement was consistently greater in the patients with mycobacteriosis kansasii, these differences were not significant. In two of the patients in this group the sputum cultures were positive for 7.8 and 9.9 years; however, they became negative within 5 months and 1 month respectively once therapy with rifampin had been started. The effects of initial therapy with rifampin in patients in whom the therapy had been uninterrupted are shown in Table V.

Discussion

The optimum duration of treatment of mycobacteriosis kansasii has not been established. However, a retrospective study is an economical and ethical method of assessing the feasibility of a long-term trial of short-course chemotherapy. Its results can also indicate the approximate length of time therapy should continue. An unsupervised program is a realistic basis from which the results can be generalized for most communities.

The success of shortening the course of tuberculosis therapy is irrefutable. Although mycobacteriosis kansasii and tuberculosis are different, rifampin has similar effects on the two diseases. We therefore felt that a closely matched comparison of patients with these diseases could show whether the course of therapy for mycobacteriosis kansasii could also be shortened. If the outcome with rifampin was good for all the patients with these disorders, then it would seem reasonable to shorten the course of therapy for mycobacteriosis kansasii.

Our patients with tuberculosis were usually sicker but improved more rapidly than those with mycobacteriosis kansasii; the greater frequency of underlying obstructive pulmonary disease in the latter may have accounted in part for the slower rate of improvement shown radiologically. The greater frequency of underlying obstructive pulmonary disease in the patients with mycobacteriosis kansasii may also help explain why the sputum smears and cultures were positive longer in this group.

Although *M. kansasii* may resemble the tubercle complex more than other mycobacteria, it is usually not as sensitive as *M. tuberculosis* to commonly used antimycobacterial drugs. Because these drugs are not as effective in treating mycobacteriosis kansasii as they are in treating tuberculosis, treatment in patients in whom this therapy was unsuccessful may be more difficult. Yet the use of rifampin shortened the clinical course in our patients with the two diseases, and all the patients with uninterrupted therapy in whom initial therapy had consisted of rifampin and two other effective drugs had a favourable outcome.

We conclude that mycobacteriosis kansasii is different enough from tuberculosis that a similar short course of chemotherapy would probably not be as likely to succeed. However, the good results of therapy for 9 to 12 months after sputum cultures become negative suggest that a prospective 9- to 12-month trial with rifampin and two other major drugs should be undertaken.

Table IV—Outcome of treatment

Outcome	No. of patients with: Mycobacteriosis kansasii	No. of patients with: Tuberculosis
Death from mycobacterial disease	0	2
Death from other cause	7	12
Residual impairment	4	2
Recurrence of disease*	1	1
Return to full-time work†	17	9

*After 8 years in the patient with mycobacteriosis kansasii and after 17 years in the patient with tuberculosis.
†The frequency in the two groups was significantly different at $p = 0.05$.

Table V—Outcome in relation to rifampin therapy*

Outcome	Patients with mycobacteriosis kansasii: Total no.	Patients with mycobacteriosis kansasii: Mean duration, wk (and SEM)	Patients with tuberculosis: Total no.	Patients with tuberculosis: Mean duration, wk (and SEM)
Positive results of sputum culture				
Without rifampin	13	31 (23)	17	9 (3)
With rifampin	16	10 (4)	13	4 (1)
Positive results of sputum smear				
Without rifampin	11	34 (27)	12	13 (4)
With rifampin	14	8 (4)	11	1 (1)
Improvement on chest x-ray film				
Without rifampin	8	33 (12)	12	17 (4)
With rifampin	13	11 (3)	10	13 (6)

*Patients in whom therapy had been interrupted or in whom rifampin had been used later were excluded.

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Precision and costs of techniques for self-monitoring of serum glucose levels

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The poor correlation between serum and urine glucose measurements has led to the development of new techniques for monitoring the blood glucose level in diabetic patients. Either a nurse or the patient can perform these tests, which involve spreading a single drop of blood onto a reagent strip. A colour change that is proportional to the serum glucose level can be read visually or with a reflectance meter. Evaluated against simultaneous serum glucose levels determined by the hospital biochemistry laboratory, those of the new techniques employing reflectance meters all showed excellent correlation (r^2 = 0.85 to 0.96). Reagent strips used without meters showed poorer correlation (r^2 = 0.69 to 0.90). The instruction given to the patients and one nurse enabled them to obtain more accurate results with one of the meters than nurses not specially trained (r^2 = 0.94 and 0.92 v. 0.85 respectively). The mean cost per glucose determination with the new techniques was 75¢, compared with $1.45 for the laboratory determinations done with automated equipment. It was concluded that the new techniques compared well with the reference method, particularly when reflectance meters were used, and that they were easily applied by the patient, as well as the medical staff, at a reasonable cost.

La piètre corrélation qui existe entre les mesures du glucose sérique et celles du glucose urinaire ont provoqué le développement de nouvelles techniques de surveillance des taux sanguins du glucose chez les patients diabétiques. Les infirmières de même que les patients peuvent pratiquer ces épreuves en étendant une seule goutte de sang sur une bande de papier réactif. Un changement de couleur proportionnel à la concentration du glucose sérique peut être apprécié soit par lecture directe ou à l'aide d'un réflectomètre. Comparées aux taux de glucose mesurés simultanément au laboratoire de biochimie de l'hôpital, les concentrations obtenues par ces nouvelles techniques et utilisant un réflectomètre ont montré d'excellentes corrélations (r^2 = 0.85 à 0.96). Les bandes de papier réactif utilisées sans réflectomètre ont montré une faible corrélation (r^2 = 0.69 à 0.90). Les directives données aux patients et à une infirmière leur ont permis d'obtenir des résultats plus précis avec un des réflectomètres que les infirmières qui n'avaient pas reçu de formation particulière (r^2 = 0.94 et 0.92 contre 0.85 respectivement). Le coût moyen de chaque glycémie était de 75¢ avec les nouvelles techniques, comparativement à $1.45 pour les déterminations du laboratoire à l'aide d'équipement automatisé. On conclut que les nouvelles techniques se comparaient favorablement à la méthode de référence, particulièrement avec l'utilisation de réflectomètres, et que celles-ci ont pu être facilement appliquées par les patients et le personnel médical, à faible coût.

Recent observations seem to implicate hyperglycemia, the hallmark of uncontrolled diabetes mellitus, in the pathogenesis of the complications of chronic diabetes.[1] Short-term studies have suggested that control of blood glucose levels can result in the regression of such complications as peripheral neuropathy and peripheral vascular disease.[2] It is therefore reasonable that the aim of treatment for diabetes should be the achievement of consistently normal glucose levels.

However, this objective is not easily attained. Many factors, such as diet, exercise, hypoglycemic agents, and the dose and timing of insulin administration affect blood glucose levels throughout the day. Associated illnesses tend to increase the blood glucose concentration. It is unlikely, then, that a fasting blood glucose test done once every 2 or 3 months would be adequate for

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