Original articles

Mycobacterium kansasii pulmonary infection: a prospective study of the results of nine months of treatment with rifampicin and ethambutol

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Abstract

Background – Pulmonary disease caused by *Mycobacterium kansasii* is reported in approximately 50 new patients in Britain annually. Rifampicin and ethambutol are effective in vitro but the optimal duration of treatment, and whether isoniazid should also be given, are uncertain. The British Thoracic Society has conducted a prospective, multicentre study of the treatment of this condition with rifampicin and ethambutol given for nine months.

Methods – One hundred and seventy three patients with two or more positive cultures and radiological evidence of disease were recruited via the Mycobacterium Reference Unit (PHLS) in Cardiff from 113 physicians in England, Scotland, and Wales. Rifampicin and ethambutol were given for nine months, other antituberculosis drugs being discontinued once the culture was identified as *M kansasii*. Patients were reviewed, sputum cultured, and chest radiographs performed before, during, and at regular intervals for 51 months after chemotherapy.

Results – The mean (SD) age was 55·5 (11·7) years, 73% were men, and 50% had other lung problems. Cavitation was seen in 88%, bilateral shadowing in 48%, and three or more lung zones were affected in 46%. All cultures were sensitive to rifampicin and ethambutol but resistant to isoniazid and pyrazinamide. One patient who took chemotherapy irregularly still had positive cultures at seven and eight months. Fifteen patients developed positive cultures after the end of chemotherapy; factors which might account for the relapse were identified in eight. Reinfection rather than relapse was suspected in three of the 15. Radiographic improvement stabilised within three years in 80%.

Conclusions – *M kansasii* pulmonary infection responds well to nine months of treatment with rifampicin and ethambutol but patients who contract this disease have a high mortality rate from other causes. Isoniazid does not appear to be a necessary part of the regimen.

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Among the opportunist mycobacteria *M kansasii* ranks second only to the *M avium-intracellulare* complex as a cause of pulmonary infection and disease. Between 40 and 70 patients are reported to the Communicable Disease Centre of the Public Health Laboratory Service each year.[1] Prior to the development of rifampicin and ethambutol, patients with *M kansasii* pulmonary infection were treated with streptomycin (S), PAS, and isoniazid (H), occasionally supplemented by pyrazinamide (Z) or ethionamide or cycloserine with variable results, some patients surviving without treatment for one to five years of observation, some responding initially but later developing intolerance to chemotherapy and deteriorating once chemotherapy was stopped, and some being cured by chemotherapy.[2] Between 15% and 60% remained sputum positive even after 24 months of chemotherapy.[3] Inclusion of rifampicin (R) and ethambutol (E) in the regimen produced relapse free cure in 92–100% of patients.[3-7] At first treatment for 18–24 months was thought to be necessary,[3 4] but subsequent retrospective studies[5 7] and one prospective study of 40 patients[6] have indicated that, when rifampicin and ethambutol form part of the regimen, the duration of chemotherapy can safely be reduced to 15, 12, or even nine months.

The British Thoracic Society has conducted a large, prospective, multicentre study of the treatment of *M kansasii* pulmonary infection with rifampicin and ethambutol for nine months.

Methods

Patients were eligible for the study if (1) their sputum was positive on culture for *M kansasii* on at least two occasions, (2) there were changes on the chest radiograph suggesting mycobacterial pulmonary infection, and (3) they were aged between 18 and 75 years. Pregnancy, coexisting terminal or preterminal disease, or the presence of *M tuberculosis* or *M bovis* in the sputum were exclusion criteria.

* The study was organised by the Opportunist Mycobacteria Subcommittee comprised of Dr P A Jenkins (Chairman), Dr J Banks, Dr I A Campbell (coordinating physician and compiler of the report), Dr A P Smith

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Table 1 Progress and events during and after chemotherapy

During chemotherapy (9 months)		After chemotherapy (51 months)	
No. starting chemotherapy	173	No. entering follow up	154
No. died	9	No. died	30*
No. absconded or not treated according to protocol	9†	No. absconded or mistakenly discharged from follow up	24
Failure of treatment	1	Relapses	15*
No. completed chemotherapy with negative cultures	154	No. completing follow up without relapse	87

* Two patients who relapsed later died; they are included in both categories.
† Ethambutol discontinued in two because of visual side effects.

When a positive *M kansasii* culture was received by the Mycobacterium Reference Unit (MRU) in Cardiff the patient's physician was contacted and two further specimens were requested and cultured in the MRU. As soon as two positive cultures were confirmed the physician was invited by the coordinator to enter the patient into the study, discontinuing antimycobacterial drugs other than rifampicin and ethambutol. Sensitivity tests using the modal resistance method of Marks were set up on all pretreatment isolates.[8] Rifampicin was given in a single daily dose of either 450 mg (patients <50 kg) or 600 mg (patients ⩾50 kg) and ethambutol in a single daily dose of 15 mg/ kg. No special steps were taken to monitor compliance. The date of starting treatment was taken as the date from which the patient first received the combination of rifampicin and ethambutol. Age, weight, occupational history, and details of previous pulmonary disease were recorded on the entry form and sent to the coordinator, together with a pretreatment chest radiograph. HIV tests were not requested.

During treatment the physician was asked to review the patient at three, seven, eight, and nine months from the time rifampicin and ethambutol were started, recording clinical progress and weight. Two specimens of sputum were requested at each review and sent to the MRU. At nine months an end of treatment chest radiograph was sent to the coordinator.

The same clinical details and two specimens of sputum were repeated at months 12, 15, 18, 24, 30, 36, 42, 48, 54, and 60, with chest radiographs at months 15, 24, 36, 48, and 60.

Failure of treatment was defined as the presence of positive cultures at any two of months seven, eight, and nine. Relapse was defined as the presence, after the end of treatment, of two or more positive cultures separated by at least two weeks in any period of three months.

The analysis was performed by the Department of Medical Statistics, University of Edinburgh.

Results
The intake extended from 1 May 1983 to 31 May 1987, during which period 173 patients (126 men, 47 women) were entered by 113 physicians in England, Scotland, and Wales. None was known to be, or suspected of being, HIV positive. The mean (SD) age of the patients was 55·5 (11·7) years and 50% gave a history of previous or current coexisting pulmonary disease. Occupational dust exposure was reported in 15%.

PRETREATMENT BACTERIOLOGY
None of the isolates was resistant to rifampicin, ethambutol or ethionamide, but 1% showed resistance to cycloserine, 2% to capreomycin, and 77% to streptomycin. All were resistant to isoniazid and pyrazinamide. A positive direct smear was found in 60%.

PRETREATMENT RADIOLOGY
Shadowing compatible with active mycobacterial pulmonary disease was noted to be bilateral in 48% of the pretreatment chest radiographs. Three or more lung zones were affected in 46%, whilst shadowing was confined to one or other or both of the upper zones in 28%. Cavitation was seen in 88% and in half of these one or more of the cavities were >2 cm in diameter. Other pulmonary, pleural, and/or cardiac diseases were evident on 61% of the chest radiographs.

RESULTS DURING AND AFTER TREATMENT
One hundred and forty nine patients initially received triple or quadruple antituberculosis chemotherapy prior to identification of the mycobacterium, at which point the regimen was reduced or altered to rifampicin and ethambutol. Twenty four patients received only rifampicin and ethambutol from the outset. The results are shown in table 1. Of the nine deaths during treatment none was related to *M kansasii* infection. In two patients ethambutol was discontinued because of unwanted effects on the visual system; both recovered fully. There was one failure of treatment (positive cultures at months seven and eight); the patient admitted that he had not taken chemotherapy regularly. The results of the sputum examinations during treatment are shown in table 2. In most instances the "no sputum" category signifies that the patient was unable to cough up any sputum, but in a few with sputum either the physician or the patient forgot to send specimens to the laboratory.

Table 2 Bacteriology during treatment

	Months of treatment			
	3	7	8	9
Culture positive (%)	11	2	0·6	0
Culture negative (%)	53	67	55	68
"No sputum" (%)	36	31	44	32
Positive smear with negative culture (%)	2	0·6	0	0·6

Only 11% still had positive sputum cultures after three months of chemotherapy.

One hundred and fifty four patients entered the post chemotherapy follow up period (table 1) of whom 30 are known to have died by the end of five years. None of the deaths was as a result of reactivation of the *M kansasii* infection although the sputum of one patient who died of respiratory failure, pneumoconiosis, chronic bronchitis/emphysema, and ischaemic heart disease was positive on culture at the review one month before death. Ten patients died from cardiovascular disease, eight from respiratory disease, seven from neoplastic disease, and two from other causes. In three patients the information was not obtained despite repeated attempts. Twenty four patients absconded from follow up or were mistakenly discharged: there was no evidence of relapse in any of these up to the point at which contact was lost. One patient produced an isolated positive culture after the end of treatment, with subsequent negative cultures thereafter.

Fifteen patients (9·7%) relapsed between six and 50 (median 23) months after the end of chemotherapy, two of whom subsequently died of other causes (these two are also counted among the 30 deaths). In eight of the 15 there appeared to be an underlying factor predisposing to relapse: four had been non-compliant with treatment, one developed carcinoma of larynx and received radiotherapy during treatment, one was on long term systemic corticosteroid therapy, one suffered from chronic cachexia and severe malnourishment, and one had allergic bronchopulmonary aspergillosis with extensive, severe bronchiectasis. In a further three patients the positive cultures were accompanied by fresh changes in the chest radiograph on the side other than that originally involved, or in a lobe different from the lobe originally involved. In the remaining four relapses fresh radiographic changes occurred in the areas which had been involved at the beginning of treatment. Only one third of the relapses had symptoms suggestive of reactivation of mycobacterial disease but loss of weight was noted in eight of the 15. All showed radiological deterioration. Of those who had received rifampicin and ethambutol alone 8·3% relapsed compared with 8·7% of those who had initially received triple or quadruple antituberculosis chemotherapy under the assumption that the condition was due to *M tuberculosis*. None of the following features at presentation were associated with relapse: age, sex, coexisting disease, extent of lung involved, cavitation.

In 114 patients good clinical progress was recorded consistently at each review date during and after chemotherapy. In eight no record was made. In 51 progress was recorded by the physician as unsatisfactory on one or more occasions, but only in 12 of these did the symptoms and signs suggest that the *M kansasii* infection was the likely cause. The mean (SD) weight gain by the end of treatment was 2·2 (4·3) kg, whilst by the end of month 60 patients were 3·6 (6·2) kg heavier than at the beginning of treatment.

RADIOLOGY DURING AND AFTER TREATMENT
A complete set of chest radiographs was available for 68 of the 87 patients who were followed for up to five years. In 80% of the patients with a full series the changes on the chest radiograph had stabilised within three years in that there were no further signs of "radiographic healing" beyond that date. Comparison of the chest radiographs at five years with the pretreatment chest radiograph showed complete clearing of the changes due to *M kansasii* in 3%, improvement but not complete clearing in 33%, and no change in the extent of disease in 64%. In those patients originally with multiple cavities, any one of which had been >2 cm in diameter, complete closure of all cavities occurred in 25%, reduction in number and shrinkage in size in 25%, while the remaining 50% were left with a cavity or cavities >2 cm in diameter. In those originally with a smaller cavity or cavities, 50% showed no residual cavitation at the end of five years.

Discussion

This prospective study includes more patients than any previous reports of *M kansasii* pulmonary infection. It confirms that the disease presents more frequently in men than in women (2·7:1), but the predominance of men was less than in earlier series.[5][6][7][9] The mean age (55·5 years) corresponded with the mean ages noted by others.[5][6][7][9] Half of our patients reported previous or current pulmonary conditions other than *M kansasii* infection, somewhat fewer than the 70% found in the Montreal survey[9] and the 66% found by Banks *et al*,[5] but much the same as that noted in Texas[6] and by Pang in Australia.[7] Association of infection with dusty work (15%) was not as obvious as might have been expected from a national survey in England and Wales[10] and a survey in Cardiff,[11] but was greater than for tuberculosis (6%).[11]

Although the frequency of cavitation (88%) was much the same, more of our patients (48%) had bilateral pulmonary involvement than did patients in previous reports,[12-14] and we did not find the marked predilection for the upper zones noted by Evans *et al*.[15] The proportion with radiographic evidence of other pulmonary disease (61%) was lower than that noted previously.[9]

Thirty nine (23%) of the 173 patients died during and after treatment but in none was *M kansasii* directly implicated as a cause of death. High death rates from causes unrelated to the *M kansasii* infection were also found by Banks *et al*[5] (37%) and Pang[7] (30%). Presumably such high rates are a function of the high prevalence of previous and coexistent diseases in the population of individuals who develop *M kansasii* infection.

The relapse rate of 9·7% is higher than that found in the only other prospective study where there was only one relapse (2·5%) among 40 patients treated with rifampicin, ethambutol, and isoniazid for 12 months, the positive cultures in that patient arising six

months after completing chemotherapy. However, only 12 of these 40 patients had been followed up for as long as five years and only 20 had been followed for three years.[6] No relapses were found among the 32 Australian patients who were treated for up to two years with various regimens, most of which contained rifampicin and ethambutol; the mean follow up from start of treatment was 64·5 months (range six months to 16 years).[7] There were no relapses in the other retrospective study, which included 30 patients followed for a mean of 5·5 years after treatment with regimens containing rifampicin and ethambutol (90%) or other combinations containing isoniazid, ethionamide, and/or cycloserine, the duration of chemotherapy varying from three to 24 months.[5]

While it is possible that relapses may have occurred among those of our patients who were lost from follow up, we feel that it is unlikely that such relapses would have escaped our attention. This infection is rare enough to warrant special comment or attention from doctors and it is the usual practice of local and PHLS microbiology laboratories to report or send *M kansasii* isolates to the MRU.

In eight of our relapsed patients there appeared to be reasons for the relapse, the chief of which was non-compliance with treatment. In three patients who relapsed after the end of chemotherapy the site of the shadowing on the chest radiograph was different from the site of the original disease; it is possible that these patients had not relapsed but were reinfected, a phenomenon strongly suspected in one of the patients reported by Pang where there had been a 12 year period free of disease.[7] *M kansasii* is a ubiquitous, low grade pathogen; patients who develop disease may well have a predisposition to mycobacterial disease, a factor which would increase the probability of reinfection. In the remaining four relapses no cause could be elicited and it must be concluded that in these individuals treatment with rifampicin and ethambutol for nine months was insufficient, as it had been in the patient on corticosteroids, the patient with malnourishment, and the patient with severe bronchiectasis and allergic bronchopulmonary aspergillosis.

Before the identification of the organism as *M kansasii* many patients (149) were given standard triple (EHR) or quadruple (EHRZ or SHRZ) antituberculosis chemotherapy for periods of 2–4 months, changing thereafter to ethambutol and rifampicin alone. The relapse rate (8·7%) among these was not significantly different from the relapse rate (8·3%) among the 24 patients who had received just ethambutol and rifampicin. When taken with the results of in vitro sensitivity testing, where 100% of the isolates were resistant to isoniazid, this observation supports the contention that it is unnecessary to include isoniazid when treating *M kansasii*. The experience of this trial and that of previous studies[5-7] would suggest that nine months of treatment with rifampicin and ethambutol is acceptable for patients with *M kansasii* pulmonary infection,

unless the patient's defences are compromised in a recognised way – for example, corticosteroid therapy, chronic severe malnutrition, or severe coexistent bronchiectasis. In such patients it would seem wise to treat for 15–24 months. Whether prolonging treatment beyond nine months would eliminate relapse among compliant patients whose defences are not obviously compromised remains a matter to be resolved by a prospective clinical trial comparing different durations of treatment; this would have to include a very large number of patients.

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