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Pulmonary disease caused by *M. malmoense* in HIV negative patients: 5-yr follow-up of patients receiving standardised treatment

The Research Committee of the British Thoracic Society

Pulmonary disease caused by M. malmoense *in HIV negative patients: 5-yr follow-up of patients receiving standardised treatment. The Research Committee of the British Thoracic Society. ©ERS Journals Ltd 2003.*

ABSTRACT: The literature concerning the management of pulmonary disease caused by *Mycobacterium malmoense* consists of retrospective reports on small series of patients. A recent multicentre trial conducted by the British Thoracic Society provided an opportunity to prospectively document the clinical features and response to treatment of this relatively rare but challenging disease in a substantial number of patients.

When two positive cultures were confirmed by the Mycobacterium Reference Units for England, Wales, Scotland or Scandinavia, the coordinating physician invited the patient's physician to enrol the patient, who was then treated on a random basis with either rifampicin plus ethambutol or rifampicin, ethambutol and isoniazid for 2 yrs. Clinical, bacteriological and radiological progress were monitored at set intervals for 5 yrs.

In over 5 yrs a total of 106 patients were recruited to the study. The mean age was 58 yrs, range 24–89 yrs. A total of 58% were male and just over half previously or at the time of the study had other lung diseases. Sputum was positive on direct smear in 58%. Cavitation was seen on the chest radiographs of 74%, the majority having cavities of $\geqslant$2 cm in diameter. Less than half of the patients showed bilateral disease, 26% having involvement of more than three lung zones. Disease was confined to the upper zone(s) in 30%. Other lung diseases were evident in 52%. Although clinical response was judged satisfactory at most reviews (90%), one in three patients died within 5 yrs and <5% were thought to have died primarily because of *M. malmoense*. There were three failures of treatment and eight relapses after the end of treatment. There was no correlation between failure of treatment/relapse and *in vitro* resistance. A total of 63 (59%) of patients were alive at 5 yrs, of whom 44 (42% of the total entry) were known to be cured.

Pulmonary disease caused by *Mycobacterium malmoense* is a serious condition that is associated with high morbidity and mortality. The results of standard susceptibility tests do not correlate with the bacteriological response of the disease to chemotherapy. Rifampicin and ethambutol, with or without isoniazid, cured only 42% of patients but were better tolerated than previously described, more complex regimens of equal or lesser efficacy. There is a need for more effective regimens that will reduce mortality and failure of treatment/relapse rates, but, in addition, attention should be directed at improving management of comorbid conditions and improving the general health of the patient.

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The British Thoracic Society has conducted a multicentre randomised trial of two regimens of chemotherapy in the treatment of lung disease caused by *Mycobacterium malmoense*, the first time such a study has been performed. Two years of rifampicin (R) plus ethambutol (E) proved equivalent to 2 yrs of R, E and isoniazid (H), with follow-up extending for 3 yrs after the end of chemotherapy [1]. The results of the two regimens have been combined and further clinical, microbiological and radiological data extracted and analysed in order to provide the first prospective survey of the long-term outcome of treatment of a large number of patients with this condition.

Design and methods

The patients studied were aged $\geqslant$16 yrs, had sputum that was positive on culture for *M. malmoense* on at least two occasions (separated by at least a week), had radiographical changes compatible with mycobacterial pulmonary disease and/or showed clinical evidence of such disease. Patients known to be positive for human immunodeficiency virus (HIV) were not included, and neither were pregnant females and those with terminal or pre-terminal disease, psychoses, previous intolerance to one or more of the trial drugs or with active co-infection from *M. tuberculosis* or *M. bovis*.

For those in whom antituberculosis chemotherapy had been started before the true diagnosis was known, drugs other than R and E were discontinued, with the exception of half the patients who also continued or received H. The daily dosages of the drugs were: R 600 mg (or 450 mg if weight <50 kg), E 15 mg·kg^{-1} and H 300 mg.

Age, sex, weight, bacilli Calmette-Guérin (BCG) status, occupational exposure to dust, any previous pulmonary disease(s) and any conditions likely to impair immune defences, *e.g.* diabetes mellitus, rheumatoid arthritis, lymphoma, leukaemia, and therapy with corticosteroids and/or immunosuppressive drugs, were recorded. The data was sent to the coordinating physician, together with the pretreatment chest radiograph. This and subsequent radiographs were read by the

coordinating physician, using a standard method of grading extent of disease and cavitation [2]. *In vitro* sensitivity tests to individual drugs (R, E, H) were performed by the Mycobacterium Reference Units (MRUs) for UK and Scandinavia, using the modal resistance method developed for *M. tuberculosis* [3, 4].

During the 2 yrs of chemotherapy the physician was asked to review the patient every 3 months, judging clinical progress as satisfactory or not, recording the patients weight and tolerance to chemotherapy and confirming their prescription. At each review two specimens of sputum were requested to be sent to the MRUs. Chest radiographs were requested at 3, 6, 12 and 24 months from the beginning of the trial. A reminder to discontinue chemotherapy was sent with the review form at 24 months. If the patient's sputum was still positive on culture at 21 months, extra specimens were collected between 21 months and 24 months. If any of these specimens proved positive the patient was categorised as a "failure of treatment" and further management was at the discretion of the physician. Patients who, despite treatment, deteriorated as a result of the mycobacterial disease and whose chemotherapy was therefore altered from that allocated were also classed as failures of treatment.

After completing chemotherapy, patients were reviewed clinically and bacteriologically (two specimens of sputum) every six months, for 5 yrs. Chest radiographs were requested annually. Those whose sputum became positive on culture (two specimens separated by $\geqslant$2 weeks) were classed as "relapses". Further management was left to the discretion of the physician.

Patients with negative cultures in the last 3 months of treatment and whose sputum remained negative upon culturing for the subsequent 3 yrs were classed as "cured".

If a patient died during the study the cause of death was ascertained from the physician and/or general practitioner and/or *post mortem* report. Using these sources, deaths were classified by the coordinating physician as caused by the mycobacterial lung disease or not.

After the trial was completed, enquiries were made of the consultant and/or general practitioner in order to ascertain whether patients that were lost during follow-up of the trial were alive after 5 yrs.

Statistical methods

Much of the study utilises simple summary statistics. The Chi-squared test for trend was used to assess the relationship between resistance of individual drugs and failure of treatment/relapse. Cox proportional hazards models were used to assess the affect of variables on patient survival. Univariate analyses were performed, plus a multivariate forward stepwise procedure, using a significance level of 0.05 for inclusion in the final model. The significance levels reported for terms in the model are those after allowance for all other terms in the model. The significance levels for the nonsignificant variables are those that resulted from their addition to the final model.

Results

A total of 106 patients (100 British, 6 Scandinavian; 58% male; 52 R and E and 54 R, E and H) were recruited in over 5 yrs (table 1). The mean age was 58 yrs, range 24–89 yrs. It was found that 55% of these patients had previous or coexisting lung disease(s), mostly chronic bronchitis/emphysema/asthma (28) and old, healed tuberculosis (22). It was also found that two patients had bronchiectasis and three had a past history of pneumonia. Conditions likely to impair immune response were noted in 14 patients (13%), whilst 21 (20%) had worked in jobs involving dust. A total of 12% were known to have been vaccinated with BCG. Sputum was positive on direct smears in 61 patients (58%).

Table 1. – Pretreatment characteristics of patients with pulmonary disease caused by *Mycobacterium malmoense*

Patient characteristics	
Sex	
Male	62
Female	44
Age mean (range) yrs	58 (24–89)
Previous lung disease	58 (55)
Reduced immunity	14 (13)
Dusty occupation	21 (20)
BCG	13 (12)
Pulmonary disease characteristics	
Positive direct smear	61 (58)
Cavitation	78 (74)
Unilateral disease	55 (52)
Only upper zone involved	32 (30)
Three zones or more involved	28 (26)
Other pulmonary disease on CXR	55 (52)

Data are presented as n (%) unless otherwise stated. BCG: bacilli Calmette-Guérin; CXR: chest radiograph.

Clinical and microbiological outcome

Clinical progress was recorded on 837 occasions, and in 751 incidences (90%) it was classed as satisfactory by the physicians. In the 86 times it was deemed unsatisfactory, 24 (3%) were attributed to the *M. malmoense* disease. There were three failures of treatment and eight relapses after the end of treatment (table 2 and fig. 1). A total of 44 patients (42%) were known to be alive and cured after 5 yrs. Of the 19 others alive at that point, 10 had previously been failures of treatment or relapses. The bacteriological status of the remaining nine could not be ascertained but none had sought treatment again from their original physician. The outcome was unknown in seven patients (table 2) and therefore, bacteriological outcome could not be ascertained in a total of 16 patients. A total of 15 patients (14%) had a poor outcome of their mycobacterial disease (failure of treatment, relapse or death because of the mycobacterial disease). On univariate analysis, increasing age (p=0.012), lower body weight (p=0.025), resistance to E (p=0.008) and involvement of more than one lung zone

Table 2. – *Mycobacterium malmoense (M. malmoense)* pulmonary disease: results during and after treatment

	R and E	R, E and H	Total
Patients n	52	54	106
Outcome unknown	3	4	7 (7)
Alive at 5 yrs	32	21	63 (59)
Deaths			
All causes	17	19	36 (34)
M. malmoense	1	3	4 (4)
Failures of treatment and relapses	6	5*	11* (10)
Completed treatment allocated and alive and cured after 5 yrs	20	24	44 (42)

Data presented as n or n (%). R: rifampicin; E: ethambutol; H: isoniazid. *: one patient died.

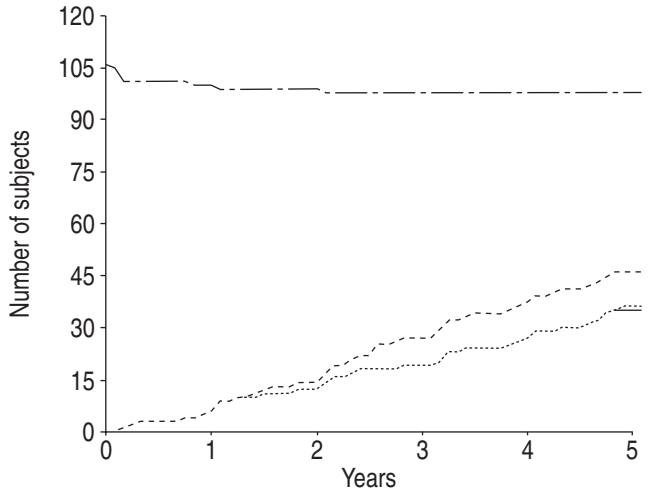

Fig. 1. – Outcome during 2 yrs of treatment and 3 yrs after treatment, showing number of patients lost from the survey (–·–·–), whether the treatment failed or the patient had a relapse (- - - -), or the patient died (·····). The difference between the solid line and the dotted line indicates the patients who died but had previously relapsed.

(p=0.009) were independent predictors of mortality. The significance of age (p=0.28) and weight (p=0.11) were lost on multivariate analysis with the Cox proportional hazards survival model, but E resistance (p=0.013) and more than one zone (p=0.002) were independent predictors of death. Weight change between 12 and 24 months significantly predicted subsequent survival (p=0.02). Each kg lost in this year increased the subsequent hazard ratio by 23%, with 95% confidence limits of 3–47%.

Outcome was unknown in seven patients (7%). By the end of 5 yrs, 36 (34%) of the patients had died, only four of whom died primarily because of the *M. malmoense* pulmonary disease. In 32 others, deaths were caused by respiratory failure not attributable to *M. malmoense* (eight), lung cancer (five), pneumonia (two), cor pulmonale (one), ischaemic heart disease (one), stroke (one), rectal cancer (one) and suicide (one). The causes of death were not available in the remaining 12 patients.

The results of *in vitro* sensitivity tests were available for 86 patients and indicated that 63% of the organisms were resistant to R and 86% were sensitive to E. Resistance was found in 82 of the 83 patients whose organisms were tested against H. There was no correlation between failure of treatment/relapse and *in vitro* resistance to these drugs (table 3).

Radiological results

The chest radiographs of 78 patients (74%) showed cavitation, 63 (59% of all patients) having at least one cavity of 2 cm or more in diameter (table 4). Disease was seen just in the upper zone(s) in 30%. A total of 55 patients (52%) had unilateral disease, whilst three zones or more were involved in 28 patients (26%). Other pulmonary diseases were evident in 55 patients (52%) and a further 12 patients had radiological signs of cardiac and pulmonary or pleural and pulmonary diseases.

Cavitation was evident in 76% of the 50 patients radiographed at 5 yrs (compared with 74% of all 106 patients on entry). In only 25% of these 50 patients did the chest radiograph at 5 yrs show a reduction in the number of lung zones involved by the scars of the disease as compared with the appearances at the beginning of treatment. The disease was judged to be radiologically healed by the end of treatment in 11% of the 45 patients with a complete set of yearly chest radiographs, by the end of the third year in 40% and after 5 yrs in 93% (table 4). In the remaining 7% of patients the appearances were worse or "not healed".

Discussion

This report gives the results of the first prospective survey of the clinical features and response to treatment of patients with *M. malmoense* pulmonary disease. Patients were treated with one of two treatment regimens, one containing R and E and the other containing R, E and H, and were followed at regular intervals during 2 yrs of treatment and for 3 yrs after treatment. A set of clinical, bacteriological and radiological assessments were performed at review period. A total of 106 patients were studied, three times greater than the number described in the two previous, retrospective, reports [5, 6]. As these reports adequately documented, the presenting symptoms and signs of this condition, which are much like those of pulmonary tuberculosis, these were not recorded in the survey.

The relationship between response to treatment and the results of standard *in vitro* susceptibility testing has been queried before [5, 6]. In this prospective examination of this relationship, the suspicions of earlier authors have been confirmed. *In vitro* resistance to antimycobacterial drugs tested singularly did not predict failure of treatment or relapse. Synergism between R and E may be one of the explanations for this finding [7]. Laboratories and clinicians need to work together to derive tests that better predict response.

Despite satisfactory clinical progress at the regular assessments, around a third of the patients died within 5 yrs, four times the expected rate within 5 yrs for the general population of a similar age. However, death was judged to be caused directly by *M. malmoense* in 4% of all patients. Such judgements regarding the precise cause of death are not always easy, especially in patients with more than one disease, but attempts were made to give accurate judgments given the circumstances of the trial. In the study by BANKS *et al.* [5], the death rate from *M. malmoense* disease (15%) was higher, although overall deaths were similar to those presented in this study and the number reported by FRANCE *et al.* [6]. In the study by FRANCE *et al.* [6], the authors observed patients for a shorter time than the present study and the study by BANKS *et al.* [5] and no patient died as a result of *M. malmoense* disease [6]. Better drugs are required to improve survival, but in addition to this, attention should be directed at improving management of comorbid conditions and general health.

Table 3. – *In vitro* susceptibility in relation to failure of treatment or relapse

	Rifampicin			Ethambutol			Isoniazid	
	Resistant	Intermediate	Sensitive	Resistant	Intermediate	Sensitive	Resistant	Sensitive
Failure of treatment/relapse	9	0	4	2	0	11	12	1
Other	45	1	27	9	1	63	70	0
Chi-squared trend	0.23			0.03				
p-value	0.63			0.82				

Table 4. – Radiological healing in the 45 patients with a complete set of radiographs

Year	Patients healed
1	3 (7)
2*	5 (11)
3	18 (40)
4	35 (78)
5	42 (93)

Data presented as n (%). *: end of treatment.

The involvement of more than one lung zone and E resistance were independent predictors of death. Having only three deaths from 27 patients with less than two lung zones involved, compared to 18 deaths from 43 patients with more extensive involvement, and the prior expectation that this variable would have prognostic value, the authors are confident of this conclusion. The evidence for the role of E resistance is less strong however, as this was an unexpected finding and multiple testing may have been responsible. There were seven deaths among the 11 patients whose cultured organisms were E resistant, and if this is confirmed in other studies, it would be important to explore this finding further.

In all except 10% of the recorded follow-up visits, patients were graded by the physicians as progressing satisfactorily during treatment. In <5% of visits unsatisfactory progress was attributed to *M. malmoense* disease. Previous authors, whilst grading more globally, found good progress was provided when R and E were in the regimen as long as they were given for a period of 18 months or longer [5, 6]. Once second- and third-line drugs were used, clinical progress was unsatisfactory, mostly due to unwanted effects of the drugs. It is difficult to compare this study's cure and survival rate (42%), prospectively derived over 5 yrs, with the previous papers as various durations and regimens have been used [5, 6]. It is sufficient to state that in the two retrospective studies, cures were associated with the use of a combination of R and E for periods much longer than is standard in the treatment of *M. tuberculosis* infection.

The results of this study showed that males predominated (58%), much as they had in the two earlier studies (60% and 65% in [5, 6], respectively). However, males were not as great a proportion of the total as they had been in a recent survey of *M. xenopi* disease [8]. The age range in the present study was 28–89 yrs with a mean of 58, which is similar to the ages reported by BANKS *et al.* [5] and FRANCE *et al.* [5] (34–82 yrs, median 62 yrs), *i.e.* mainly a middle-aged-to-elderly population, as is true with the other species of opportunist mycobacteria [8–10]. Older patients tended to do less favourably than the younger patients in terms of survival which was not an unexpected finding as it was also found with *M. avium* intracellular complex (MAC) pulmonary disease [10]. However, in contrast to MAC, age did not predict outcome. The prevalence of underlying lung disease (55%) was not as great as previously observed for *M. malmoense* (66–84%) [5, 6], but is in line with more recent descriptions of disease caused by *M. kansasii*, *M. xenopi* and MAC, the majority having chronic bronchitis and/or emphysema [8–10]. Such pulmonary compromise, taken with other comorbid conditions, is likely to preclude surgery as a therapeutic option for many patients. Conditions associated with reduced immune responses were found in 13%, similar to the proportion found by BANKS *et al.* [5] but not as large as the 32% in the review by FRANCE *et al.* [6]. The proportion of patients with *M. malmoense* disease who had conditions that could suppress immune responses was half the proportion found recently in *M. xenopi* patients [8] but did not differ greatly from those found in MAC patients [10]. None of the patients in this study were known to have HIV infection on entry to the study and none were known to have developed such infection during the study. *M. malmoense* infection is very rare in patients with HIV infection and tends to occur late in the progression of acquired immunodeficiency syndrome (AIDS) [11, 12]. In contrast to this study's findings with MAC, an occupation involving dust was not a predictor of death within 5 yrs.

Three quarters of the patients had cavitation, a smaller proportion than the 95–100% seen in the two retrospective series [5, 6]. Cavitation was noted in 88% of *M. kansasii* infections [9], 81% of *M. xenopi* infections [8] and 61% of MAC infections [10], with large cavities also predominating in other opportunist mycobacterial lung infections. Over half of the patients in this study had unilateral disease as did those of BANKS *et al.* [5]. The authors of this study have found that the extent of the disease was related to survival, a new but unsurprising observation true also of MAC disease [10]. FRANCE *et al.* [6] commented that the radiological changes they observed were indistinguishable from *M. tuberculosis* [6] and EVANS *et al.* [13] noted differences but stated that they were not sufficient to allow a specific diagnosis. The observations of this study are in keeping with these findings. Cavitation was still evident at 5 yrs in 76%, a proportion higher than found with MAC (43%) [10] but very similar to that with *M. xenopi* (70%) [8]. Appearances were classed as radiologically healed in 93% of patients at 5 yrs, which was similar for *M. xenopi* [8] and MAC [10]. Reduction in the number of lung zones with evidence of involvement (residual scarring and/or cavitation) was observed in a quarter of the patients, as compared with 36% for *M. xenopi* [8] and 23% for MAC [10].

This prospective, long-term study has confirmed that the results of *in vitro* resistance/sensitivity tests do not predict bacteriological response to treatment in pulmonary disease caused by *Mycobacterium malmoense*. It is therefore important to assess new drugs in randomised, controlled clinical trials rather than rely on results of such tests. The combination of rifampicin and ethambutol has a better therapeutic ratio than more complex regimens, but there is a clear need for more effective treatments that will reduce the 5-yr mortality (34%) and failure of treatment/relapse (10%) rates. There could be scope further improve survival by better management of comorbid conditions and by improving the general health of the patient. It may be that macrolides and/or quinolones, which, during the period of this study, were found to have *in vitro* activity against opportunist mycobacteria [14–18], will result in better cure rates when added to rifampicin and ethambutol. The British Thoracic Society's ongoing multicentre trial should answer this question by the end of 2004.

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