

First randomised trial of treatments for pulmonary disease caused by *M avium intracellulare*, *M malmoense*, and *M xenopi* in HIV negative patients: rifampicin, ethambutol and isoniazid versus rifampicin and ethambutol

Research Committee of the British Thoracic Society

Abstract

Background—The treatment of pulmonary disease caused by opportunist mycobacteria is controversial. It is uncertain whether in vitro sensitivity testing predicts clinical response in the way it does for *Mycobacterium tuberculosis*. The literature suggests that the combination of rifampicin (R) and ethambutol (E) is important whereas isoniazid (H) may not be, but to date there have been no published reports of randomised controlled trials in the treatment of these conditions. The British Thoracic Society has conducted the first such trial, a randomised study of two regimens in HIV negative patients with pulmonary disease caused by *M avium intracellulare* (MAC), *M malmoense*, and *M xenopi*.

Methods—When two positive cultures were confirmed by the Mycobacterium Reference Laboratories for England, Wales and Scotland, the coordinating physician invited the patient's physician to enrol the patient. Patients were also recruited from Scandinavia. Randomisation to 2 years of treatment with RE or REH was performed from lists held in the coordinator's office. Clinical, bacteriological, and radiological progress was monitored at set intervals up to 5 years.

Results—From October 1987 to December 1992, 141 physicians entered 223 patients (106 with *M malmoense*, 75 with MAC, 42 with *M xenopi*). At entry the RE and REH groups were comparable over a range of demographic and clinical features. For each species there was no significant difference between RE and REH in the number of deaths, but when the three species were combined there were fewer deaths from the mycobacterial disease with RE (1% v 8%, $p=0.018$, odds ratio 0.10, exact 95% CI 0.00 to 0.76). For *M malmoense* the failure of treatment/relapse rates did not differ appreciably between the regimens, but for MAC there were fewer failures of

treatment/relapses with REH (16% v 41%, $p=0.033$). With *M xenopi* there was a non-significant trend in the same direction (5% v 18%, $p=0.41$) and when all three species were combined there was a significant difference in favour of REH (11% v 22%, $p=0.033$). There was no correlation between failure of treatment/relapse and in vitro resistance. *M xenopi* was associated with the greatest mortality (57% at 5 years), MAC was the most difficult to eradicate, and *M malmoense* had the most favourable outlook (42% known to be alive and cured at 5 years).

Conclusions—The results of susceptibility tests performed by the modal resistance method do not correlate with the patient's response to chemotherapy. RE and REH are tolerated better than previous regimens containing second or third line antimycobacterial drugs. Treatment of *M malmoense* with RE for 2 years is preferable to REH. The addition of H reduces the failure of treatment/relapse rates for MAC and has a tendency to do so also for *M xenopi*, but there is a suggestion that REH is associated with higher death rates overall. Better regimens are required.

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Keywords: opportunist mycobacteria; isoniazid; rifampicin; ethambutol; treatment regimens; *Mycobacterium avium intracellulare*; *Mycobacterium malmoense*; *Mycobacterium xenopi*

The literature describing the treatment of pulmonary infection by opportunist mycobacteria in HIV negative patients consists largely of retrospective reports of the results of treatment with various antimycobacterial regimens, given mostly to small numbers of patients.^{1–11} There have been no reports of prospective randomised controlled trials. Consequently, even though guidelines have been published,¹² there is no consensus about which drugs should be used nor about the optimal duration of treatment. The confusion is compounded by a

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seemingly paradoxical lack of correlation between the clinical response and the results of conventional in vitro susceptibility tests of single antimycobacterial drugs.^{5 6 8 9 13}

In some of the retrospective series it was apparent that patients did better when first line antituberculosis drugs were used than when patients were treated with regimens which were based on the results of sensitivity testing and which included second line drugs.^{4-6 8 9 14} Toxicity from such reserve drugs and lack of compliance are likely to be partial explanations for these findings but the work of Heifets,¹⁵ Banks and Jenkins,¹⁶ and of Hoffner *et al*¹⁷ indicated synergy between rifampicin and ethambutol and explains why regimens containing these two drugs were successful, even when there was resistance in vitro to each drug when tested singly against the organism. These authors also found that, although streptomycin sometimes interacted synergistically with ethambutol (E) and rifampicin (R), isoniazid (H) did not appear to do so, which raised the question as to whether H confers any therapeutic advantage when added to R and E.

Against this background the Research Committee of the British Thoracic Society has conducted the first prospective randomised controlled trial in HIV negative patients infected with *M avium intracellulare* (MAC), *M malmoense*, or *M xenopi*. The aim was to compare the regimen of rifampicin, ethambutol and isoniazid (REH) with the regimen of rifampicin and ethambutol (RE), the duration of chemotherapy being 2 years with follow up for 3 years after the end of chemotherapy. In addition to being a multinational (Britain and Scandinavia) clinical trial, the study serves as the first prospective survey of the long term outcome of treatment of patients with pulmonary disease caused by these mycobacterial species.

Methods

PATIENTS

Patients were eligible for inclusion in the study if (1) they were aged 16 years or over; (2) the chest radiograph showed changes compatible with mycobacterial disease and/or there was clinical evidence of mycobacterial pulmonary disease; (3) the sputum was positive on culture for MAC, *M malmoense*, or *M xenopi* on at least two occasions; (4) they were not known to be HIV positive; and (5) they gave informed consent.

Pregnant women and patients with terminal or pre-terminal disease, psychoses, previous intolerance to one or more of the trial drugs, or with active co-infection by *M tuberculosis* or *M bovis* were not included in the study. HIV tests were not requested but patients known to be HIV positive were excluded from the study. In Britain the Mycobacterium Reference Unit (MRU) for England and Wales and the MRU for Scotland informed the coordinator once two positive isolates were obtained from a patient. The coordinator contacted the patient's physician and informed him/her of the trial. Once the physician and patient agreed to enter the trial, treatment was allocated cen-

trally by the coordinator from separate randomisation lists for each of the three species. Scandinavian physicians contacted the coordinator directly.

The physician was asked to discontinue any antimycobacterial drugs other than those to which the patient had been allocated, and to complete and return an entry form giving details of the patient's age, sex, weight, BCG status, occupational exposure to dust, any previous pulmonary disease(s), and any conditions likely to impair immune defences such as diabetes mellitus, rheumatoid arthritis, lymphoma, leukaemia, treatment with corticosteroids and/or immunosuppressive drugs. On that form the physician also confirmed the dosages of the trial drugs as follows:

- Rifampicin 450 mg (or 600 mg in those weighing ≥ 50 kg) orally once daily.
- Ethambutol 15 mg/kg orally once daily.
- Isoniazid 300 mg orally once daily.

Patients weighing 50 kg or less were asked to take their tablets on an empty stomach. The protocol did not request directly observed therapy. Decisions about inpatient or outpatient management were left to the physician. The pretreatment chest radiograph was sent to the coordinator together with the entry form. This and subsequent radiographs were read by the coordinating physician using a standard method of grading extent of disease and cavitation, and unaware of the regimen which the patient had received. In vitro sensitivity tests to individual drugs (rifampicin, ethambutol, isoniazid) were performed by the MRUs using the modal resistance method developed for *M tuberculosis* and used by laboratories in the UK and Scandinavia.^{18 19}

During chemotherapy the physician was asked to review the patient every 3 months, recording clinical progress, weight, tolerance to chemotherapy, and confirmation of its prescription. Two specimens of sputum were requested on or around these dates, to be sent to the MRUs. Chest radiographs were requested at 3, 6, 12, and 24 months from the beginning of the trial regimen. 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 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 their 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 6 months up to 5 years. Chest radiographs were requested annually. Those whose sputum became positive on culture (two specimens separated by at least 2 weeks) were classed as relapses. Further treatment was left to the discretion of the physician.

If a patient died during his/her period in the study the cause of death was ascertained from

Table 1 Pretreatment characteristics of treatment groups

	<i>M malmoense</i> (n=106)		<i>MAC</i> (n=75)		<i>M xenopi</i> (n=42)		<i>All three species</i> (n=223)	
	RE (n=52)	REH (n=54)	RE (n=37)	REH (n=38)	RE (n=22)	REH (n=20)	RE (n=112)	REH (n=111)
Sex (M/F)	34/20	29/24	21/16	19/19	18/4	14/6	71/41	63/48
Mean (SD) age (years)	57.2 (14.1)	58.4 (13.4)	63.4 (13.7)	65.1 (11.2)	66.9 (8.5)	62.6 (13.7)	61.3 (13.4)	61.6 (13.0)
Previous lung disease(s)	31	27	21	25	14	14	66	66
Reduced immunity	7	7	1	5	5	6	13	18
Exposure to dust	11	10	4	8	4	3	19	21
BCG	6	7	3	4	0	1	9	12
Direct smear +ve	28	33	21	21	13	13	62	67
Cavitation	40	38	21	25	19	15	80	78
≥ 3 zones	14	14	13	11	8	7	35	32
Other pulmonary diseases on chest radiograph	29	26	18	22	14	13	61	61

RE = rifampicin + ethambutol; REH = rifampicin + ethambutol + isoniazid.

the physician and/or general practitioner (GP) and/or report of the post-mortem examination. Using these data, deaths were classified by the coordinating physician as being caused either by opportunist mycobacterial pulmonary infection or not being so caused.

STATISTICAL ANALYSIS

Comparisons of the two randomised treatment groups have been undertaken for each of the mycobacterial subgroups and also for the total data set. The statistical methods applied are all standard, and the analysis was primarily undertaken using SAS Version 6.12 supplemented by EpiInfo Version 6.04c. There were no formal power calculations undertaken before the commencement of the trial, which is the first randomised controlled trial in this area of research. Recruitment took place over 5 years and the decision to stop recruiting was made independently of efficacy data, as a compromise between maximising trial input and financial constraints.

Results

Between 1 October 1987 and 31 December 1992, 141 physicians from England, Scotland and Wales, Denmark, Finland, Norway and Sweden entered 223 patients, 106 with disease caused by *M malmoense* (52 RE, 54 REH), 75 with *MAC* (37 RE, 38 REH), and 42 with *M xenopi* (22 RE, 20 REH). The RE and REH groups were not appreciably different in any of the following characteristics: mean age, sex distribution, exposure to dust, previous lung diseases, conditions likely to impair immune response, previous BCG vaccination, sputum smear positivity, radiological extent of disease, cavitation and other pulmonary diseases evident on the chest radiograph (table 1).

In 49 patients (24 RE and 25 REH; table 2) the protocol was not followed: 12 received treatment different from that allocated because of unwanted effects from E, six because of unwanted effects from H, four because of unwanted effects from R; in the remaining 27 patients treatment varied from that allocated or was discontinued prematurely by the physician or GP (none because of HIV/AIDS) or the patient defaulted from follow up. In all of these respects there were no differences between the RE and REH groups neither within species nor overall.

For each species of opportunist mycobacteria there were no statistically significant differences between the RE and REH regimens in the number of deaths during the study (table 2). Overall there were 74 deaths (32 RE and 42 REH), a difference which was not significant at the 5% level ($\chi^2 = 1.8$, $p=0.18$, odds ratio (OR)=0.66, 95% CI 0.36 to 1.20). Of the 64 patients who died from causes other than mycobacterial disease, 20 died of respiratory failure, 13 of lung cancer, nine of pneumonia, eight of ischaemic heart disease, one of cor pulmonale, and seven of other causes (none due to AIDS or drug toxicity). In six patients the cause of death was uncertain.

Within each species the number of patients who died because of mycobacterial disease did not differ significantly between treatment groups, but when the three species were combined there were significantly fewer deaths resulting from mycobacterial disease in the RE group than in the REH group: 1% v 8% (Fisher's exact test, $p=0.018$, OR=0.10, exact 95% CI 0.00 to 0.76).

For *M malmoense* the numbers classified as failures of treatment and as relapses did not

Table 2 Results during and after treatment

	<i>M malmoense</i> (n=106)		<i>MAC</i> (n=75)		<i>M xenopi</i> (n=42)		<i>All three species</i>		Total
	RE	REH	RE	REH	RE	REH	RE	REH	
No entered	52	54	37	38	22	20	112	111	223
No deviated from protocol	15 ^{1D}	12 ^{1D}	6	8	3	5	24 ^{1D}	25 ^{1D}	49 ^{2D}
No of deaths from all causes	12 ^{1W}	15 ^{1R1W}	9 ^{3F}	14 ^{2F1R}	11 ^{1F}	13 ^{1F}	32 ^{4F1W}	42 ^{3F2R1W}	74 ^{7F2R2W}
No died because of mycobacteria	1	3	0	3	0	3	1*	9*	10
No of failures of treatment and relapses	3 + 3 (6)	0 + 5 (5) ^{1D}	7 ^{3D} + 8	4 ^{2D} + 2 ^{1D}	2 ^{1D} + 2 (4)	1 ^{1D} + 0 (1)	12 ^{1D} + 13	5 ^{3D} + 7 ^{1D}	37 ^{9D}
No who completed treatment as allocated and were alive and cured at 5 years	20	24	10	13	5	2	35	39	74

* $p = 0.018$ (Fisher's exact test); † $\chi^2=4.5$; $p=0.033$; ‡ $\chi^2=4.5$; $p=0.033$

Superscripts show patients represented in other categories: W = deviated from protocol; F = failure of treatment; R = relapse; d = death
RE = rifampicin + ethambutol; REH = rifampicin + ethambutol + isoniazid.

Table 3 Relationship of outcome to in vitro drug susceptibility

Drug susceptibility	No of strains	No (%) failures of treatment and relapses
Rifampicin		
Sensitive	58	8 (14%)
Intermediate	3	1 (33%)
Resistant	113	24 (21%)
Ethambutol		
Sensitive	101	15 (15%)
Intermediate	10	3 (30%)
Resistant	63	15 (24%)
Isoniazid		
Sensitive	1	0
Intermediate	0	0
Resistant	83	12 (14%)

differ appreciably between the RE and REH groups, but in patients with MAC there were fewer failures of treatment/relapses in the REH group ($\chi^2 = 4.5$; $p=0.033$). For *M. xenopi* there was a trend in favour of REH but this did not reach statistical significance ($p=0.41$). When all RE failures/relapses (22%) were compared with all REH failures/relapses (11%), a significant difference emerged in favour of REH ($\chi^2 = 4.5$; $p=0.033$). The differences between those classified as alive and cured were not significant at the 5% level, neither within species nor for RE versus REH overall.

Pretreatment susceptibility results were available for R in 174, E in 174, and for H in 84 strains. There was no correlation between failure of treatment/relapse and in vitro resistance nor between cure and in vitro sensitivity (table 3).

Clinical progress, weight gain, and radiological improvement did not differ between RE and REH groups for any of the three species, nor when the three species were combined. Records of clinical progress were available from 1707 clinical encounters during and after treatment: in 88% these records indicated satisfactory clinical progress. Unsatisfactory progress was recorded on 12% of occasions but only a third of these were attributed to the opportunist mycobacterial lung disease. Mean (SD) weight gain to 5 years was 1.16 (6.96) kg by which time 25% of those with a complete series of chest radiographs showed closure of cavities and/or reduction in the extent of disease.

In order to provide overall outcome data for each species, the two treatment groups were combined within each species (table 4). Disease caused by *M. xenopi* was associated with the highest 5 year mortality. MAC was more difficult to eradicate than the other two species. More patients with *M. malmoense* were alive and cured at the end of 5 years than with the other two species.

Table 4 Outcome at 5 years of treatment of *M. malmoense*, MAC, and *M. xenopi* for 2 years with RE or REH

Outcome	<i>M. malmoense</i> (n=106)	MAC (n=75)	<i>M. xenopi</i> (n=42)	All 3 species (n=223)	p value*
Deviated from protocol	25%	19%	19%	22%	0.51
Died (all causes)	25%	31%	57%	33%	0.001
Died because of mycobacteria	4%	4%	7%	4%	0.65
Failure of treatment or relapse	10%	28%	12%	17%	0.004
Alive and cured	42%	31%	17%	33%	0.015

*The percentages in each column do not add up to 100% because some patients fell into more than one category. An overall significance test is therefore not possible and for each row the χ^2 significance test compares the three percentages.

Discussion

This is the first randomised trial of the treatment of pulmonary disease caused by opportunist mycobacteria. It is unique, not only in this respect, but also as the first large long term prospective survey of these conditions. It has demonstrated that a simple, relatively non-toxic, regimen can achieve results as good as any previously described with regimens which contained five or six drugs and were not well tolerated.

In the reports of some of the retrospective studies attention has been drawn to the fact that the in vivo response did not appear to be related to the results of in vitro susceptibility tests in the way that it is for *M. tuberculosis*.^{4-6 8 9 13 14} This prospective, relatively large, study has confirmed that the results of such tests, using single antimycobacterial drugs and performed by the standard modal resistance technique,^{18 19} do not predict the clinical and bacteriological response. Until levels of in vitro resistance that correlate with clinical outcome are defined, giving in vitro susceptibility results to clinicians is likely to confuse treatment rather than aid it. Laboratories may well wish to rethink not only how they report the results to the clinicians, but also how they perform the tests.

Although for each species the difference between the RE and REH regimens in respect of deaths caused by the opportunist mycobacteria, favouring the RE group, did not reach statistical significance, when all three species were combined RE emerged as the superior regimen on this criterion. However, this difference must be interpreted with caution: attributing the cause of death was a matter of judgement between the coordinating physician, the patient's physician and/or GP, none of whom was blind to the treatment received by the patient when deciding cause of death. Precise decisions about cause of death are not always easy and in some instances there will be an element of subjective judgement. When the regimens were compared according to the more objective outcome measure "failure of treatment/relapse", the overall difference went the other way, favouring the REH group rather than the RE group ($p=0.033$). This emerged particularly for the patients with MAC in whom REH was significantly superior to RE, whereas in those with *M. xenopi* or *M. malmoense* the differences were not statistically significant. The results of this trial indicate that isoniazid has little or no place in the treatment of *M. xenopi* or *M. malmoense*. It is of use in MAC but, in view of the possibility that it might be associated with a higher death rate,

perhaps it should only be added if RE is failing to render the sputum negative on culture.

The results of treatment compared favourably with those reported in the retrospective studies in the literature,^{1-11 13 14 20} although neither regimen produced high cure rates. The relatively high death rates and failure/relapse rates we have found may be partially explained by the age of the patients and the high prevalence of pre-existing clinical and/or radiological lung disease, all factors which might reduce the patient's response to the infection. Relatively few patients were unable to tolerate treatment because of unwanted effects of the drugs, in contrast to the high intolerance rates reported in studies where second line or third line antimycobacterial drugs had been used because of the results of in vitro susceptibility tests.^{4 5 10 20} Failure/relapse rates for MAC were less than those observed by Huang *et al*²⁰ and were also less than those reported by Dutt and Stead who used five drugs \pm surgery.³ Hunter *et al*, reporting results of regimens containing REH or streptomycin, PAS and H, obtained results much like ours.⁴ For *M malmoense* the results were little different from those reported by Banks *et al*⁶ and by France *et al*⁶ for regimens containing ER, but were better than the results they found with second or third line drugs. *M xenopi* infection was associated with high overall mortality in this trial as it was in the previous reports, although only 7% of deaths were attributed to the organism compared with 10–20% in the earlier series.^{9 10}

While the trial was in progress the macrolide and quinolone agents clarithromycin and ciprofloxacin were shown to have in vitro activity against opportunist mycobacteria.²¹⁻²³ There have been reports of their efficacy in vivo,^{21 24-28} but randomised clinical trials which demonstrate efficacy have only been reported for MAC disease in HIV positive patients.²⁹⁻³¹ The Research Committee of the BTS is currently conducting a further multicentre randomised trial to assess the value of clarithromycin and of ciprofloxacin in the treatment of pulmonary disease in HIV negative patients; a regimen of 2 years of rifampicin, ethambutol, and clarithromycin is being compared with 2 years of rifampicin, ethambutol, and ciprofloxacin. In addition, there is an optional arm where patients can be further randomised to receive immunotherapy with *M vaccae* (SRL 172) or to no immunotherapy. That study, as the one reported here, will use the hard end points of death, failure of treatment, and relapse rather than the surrogate measures of outcome reported in recent uncontrolled studies.^{27 28} It is hoped that these new regimens will improve cure rates but, in the meantime, the evidence from this study indicates that a regimen of RE for 2 years offers a better chance of successful outcome in patients with *M malmoense* or *M xenopi* than REH for 2 years. For those with MAC the addition of H will reduce failure/relapse rates but this three drug regimen may possibly be associated with an increased death rate. The final results of this randomised controlled trial will allow the Joint Tuberculosis Committee to reclassify the relevant recommendations in the 1999 guidelines

on management of opportunist mycobacterial infections from grade B to grade A.³²

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