Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in the treatment of Opportunist Mycobacterial pulmonary diseases and an assessment of the value of immunotherapy with M.vaccae: a pragmatic, randomised trial by The British Thoracic Society.

**RESEARCH COMMITTEE OF THE BRITISH THORACIC SOCIETY.**

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Abstract

Background

The management of pulmonary disease caused by opportunist mycobacteria is bedevilled by a lack of randomized trials to provide an evidence-base for treatment. Rifampicin (R) and ethambutol (E) are the mainstay of treatment but the roles of macrolides and quinolones are not clear, nor is the role of immunotherapy with M. vaccae

Aims

This trial was designed to compare clarithromycin (Clari) and ciprofloxacin (Cipro) as third drugs added to two years of rifampicin and ethambutol as treatment for pulmonary disease caused by M. avium-intracellulare (MAC), M. malmoense and M. xenopi. There was also an optional comparison of immunotherapy with M. vaccae with no immunotherapy.

Methods

Patients with pulmonary disease caused by these organisms were recruited to the trial once two positive cultures were confirmed. A factorial design permitted comparisons of clarithromycin and ciprofloxacin as well as immunotherapy/no immunotherapy. Information on clinical and bacteriological progress was obtained annually during the two years of treatment and for three years thereafter. If the patient was not improving at 1 year, the regimen was supplemented by the addition of the drug which he/she had not received in the original allocation of treatment.

Results

Three hundred and seventy-one patients (186 REClari, 185 RECipro) were entered by 191 physicians, 170 with MAC, 167 with M. malmoense and 34 with M. xenopi. Optional immunotherapy randomization was chosen by 170 patients of whom 84
received *M. vaccae*. No significant differences in outcomes were found between *M. vaccae*-treated patients and those who had not been randomised to *M. vaccae*. These patients were combined with the remaining 201 for purposes of comparison of REClari with RECipro.

All cause mortality was high for both groups (44% REClari, 43% RECipro). In patients with MAC the all-cause death rates were higher with REClari (48%) than with RECipro (29%), whereas for *M. malmoense* (42% vs 56%) and *M. xenopi* (29% vs 47%) the rates were higher with RECipro (p=0.006). Most strikingly, only 3% died because of their mycobacterial disease (REClari = RECipro). At the end of treatment 4% of REClari and 10% of RECipro patients still had positive cultures. Among those with negative cultures at end of treatment 6% of REClari and 4% of RECipro patients relapsed. At 5 years 30% of REClari patients were known to have completed treatment as allocated and to be alive and cured, compared with 21% of the RECipro group (p=0.04), but this difference was principally due to those with *M. malmoense* (REClari 38%, RECipro 20%).

Patients with MAC or *M. xenopi* were more likely to have poor outcome (death due to mycobacterial disease, failure of treatment or relapse) than those with *M. malmoense* (p=0.004), there being no difference between REClari and RECipro in this respect. Overall, 20% in each group were unable to tolerate the regimen allocated, Cipro being associated with a trend towards more unwanted effects (16%) than Clari (9%), p=0.05.

**Conclusion**
Considering all three species together, there were no differences in outcome between the REClari and RECipro groups. Immunotherapy did not improve outcome. Mortality rates were high but only a small proportion died because of their mycobacterial disease. For *M. malmoense* and *M. xenopi* REClari appeared preferable to RECipro, whereas for MAC the opposite was true. Patients with MAC or *M. xenopi* had worse outcomes than those with *M. malmoense*, but there was no significant difference between REClari and RECipro. Comparison with other studies suggest that these triple-drug regimens, whilst having much the same beneficial effects as RE alone, resulted in twice as many unwanted effects and are consequently likely to reduce concordance. New therapies, optimised management of co-morbid conditions and a more holistic approach must be explored in the hope of improving outcome.
Introduction

In 2001 the Research Committee of the British Thoracic Society (BTS) published the results of the first ever, prospective, randomised trial of treatments for pulmonary disease caused by the opportunist mycobacteria, *M. avium intracellulare scrofulaceum* (MAC or MAIS), *M. malmoense* and *M. xenopi*. That trial showed that two years of treatment with rifampicin (R) and ethambutol (E) or with R+E+isoniazid (H) achieved results comparable with those reported with previous regimens, which often contained five or six antimycobacterial drugs, but with considerably fewer problems from drug intolerance\(^1\). The REH regimen reduced failure/relapse rates more than RE but was associated with an increased death rate from the mycobacterial disease. While the trial was in progress the macrolide and quinolone agents, clarithromycin (Clari) and ciprofloxacin (Cipro) were shown to have in vitro activity against opportunist mycobacteria\(^2,3\). There had been reports of their efficacy in vivo\(^2,4-8\) but randomised clinical trials which demonstrated efficacy had only been reported for MAC in HIV positive patients\(^9-11\). The Research Committee of the BTS has conducted a further, multi-centre, prospective, randomised, international, open-label pragmatic trial to assess the values of Clari and of Cipro in the treatment of opportunist mycobacterial pulmonary disease in patients who were not known to be HIV positive: REClari for two years vs RECipro for two years. In addition, because of evidence emerging at the time\(^12,13\) there was an option in the trial where patients could be further randomised to receive immunotherapy with *M. vaccae* (SRL 172)\(^12\) or to no immunotherapy.
Methods
Patients

Patients were eligible for inclusion in the study if 1) they were aged 16 years or over; 2) they had clinical and/or radiological evidence of active mycobacterial disease; 3) sputum was positive on culture for MAC, *M.malmoense* or *M.xenopi* on at least two occasions a minimum of a week apart 4) they were not known to be HIV positive; 5) they gave informed consent.

Pregnant women and women of childbearing age not taking adequate contraceptive precautions and patients who had sputum currently positive on culture for *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.

The Regional Centres for Tuberculosis (TB) Bacteriology in Cardiff, Birmingham and Newcastle, the Mycobacterium Reference Unit (MRU) Dulwich and the Scottish Mycobacterium Reference Laboratory, City Hospital, Edinburgh informed the co-ordinator of the trial when two positive isolates were obtained from a patient. The co-ordinator 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 centrally by the co-ordinator from separate randomisation lists, based on randomised permuted blocks, for each of the three species. Scandinavian and Italian physicians contacted the co-ordinator directly, as did the occasional physician in Britain. A factorial design was used for patients agreeing to enter the immunotherapy limb of the trial, so that for these patients there were four possible treatments:

a) RECipro b) RECipro + M.vaccae 4 times in first 6 months
c) REClari
d) REClari + M.vaccae 4 times in first 6 months

Patients choosing not to enter the immunotherapy limb of the trial were randomised between RECipro and REClari.

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, previous pulmonary disease(s) and date of start of treatment with the trial regimen. 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 or more) orally once daily;
Ethambutol: 15 mg per kg orally once daily;
Clarithromycin: 500 mg b.d.;
Ciprofloxacin: 750 mg b.d.;
M.vaccae 0.1 ml intradermally on entry and every two months up to six months (ie. four doses in all).

Patients weighing less than 50 kg were asked to take their tablets on an empty stomach. Decisions about in-patient or out-patient management were left to the physician and the protocol did not request directly observed therapy.

The pre-treatment chest radiograph was sent to the co-ordinator with the entry form. This was read by the co-ordinating physician using a standard method of grading extent of disease and cavitation and unaware of the regimen the patient had received\(^1\).
During chemotherapy the physician was asked, for purposes of the trial, to review the patient at 12 and 24 months, recording clinical progress, weight, tolerance to chemotherapy and confirmation of its prescription on forms sent by the co-ordinator. If the sputum at twelve months proved positive on culture, the Regional/National Laboratory notified the co-ordinator and the patient’s physician who was then required to add the fourth drug (Cipro to those on REClari or Clari to those on RECipro). A reminder to discontinue chemotherapy was sent with the review form at twenty four months. Patients whose sputum was still positive on culture on two occasions, separated by an interval of at least two weeks, in the last three months of treatment, were classed as failures of treatment. 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 the patient had completed chemotherapy, the physician was asked to report, by means of pre-sent review forms, clinical and bacteriological status (2 specimens of sputum) every 12 months for a further 3 years, i.e. up to five years from entry to the trial. Those whose sputum became positive on culture (2 specimens separated by at least two weeks) were classed as relapses. Further treatment was left to the discretion of the physician.

If the patient died during his/her period in the study, the cause of death was ascertained from the physician and or general practitioner (GP) and/or a report of the post-mortem examination. Using these data, deaths were classified by the co-ordinating physician as being caused either by opportunist mycobacterial pulmonary
disease or not being so caused and were analysed as “all-cause” mortality and as mortality directly attributed to the mycobacterial disease.

Statistical analysis

The statistical methods applied are all standard, and the analysis, based on intention-to-treat, was undertaken using SPSS version 13 and SAS version 9.1. There were no formal power calculations undertaken before the commencement of the trial. It was regarded as a study to estimate the magnitude of differences between the treatment arms with as much precision as numbers permitted over the period of the trial. Recruitment took place over five years and the decision to stop recruiting was made independently of efficacy data, as a compromise between maximising trial input and financial constraints. Primary end-points for analysis were a) death due to mycobacterial disease b) failure of treatment and c) relapse. Secondary end-points were i) all-cause mortality, ii) unwanted effects of chemotherapy and/or immunotherapy, iii) a combination of (a), (b) and (c) into a composite measure of “poor outcome”, iv) a composite measure of “good outcome” defined as completing treatment as allocated and alive and cured at the end of five years, v) clinical progress as recorded over the follow-up points during the trial and vi) number of patients requiring addition of the fourth drug and outcome in those patients.
Results

Recruitment and randomisation

Between March 1995 and September 1999, 191 physicians from England, Scotland, Wales, Denmark, Finland, Norway, Sweden and Italy entered 386 patients, of whom 15 did not fulfil the criteria for eligibility for the trial, leaving 371 patients for analysis (MAC 170; *M.malmoense* 167; *M.xenopi* 34). Of these, 201 opted not to enter the immunotherapy randomisation and were randomised just between REClari and RECipro (Table 1). The remaining 170 patients chose to enter the immunotherapy limb and were randomised between REClari and RECipro as well as between *M.vaccae* and no *M.vaccae*, 84 patients receiving *M.vaccae* and chemotherapy whilst 86 received chemotherapy but no *M.vaccae* (Table 2).

In the 201 patients who elected not to enter the immunotherapy limb, the REClari and the RECipro groups were not appreciably different in any of the following characteristics: mean age, previous BCG vaccination, radiological extent of disease, cavitation and evidence of other pulmonary disease on the chest radiograph though a higher proportion of men were randomised to REClari (Table 1). The distributions for patients randomised to immunotherapy (84) or no immunotherapy (86) were similar except for an excess of patients in the immunotherapy arm with BCG vaccination and an excess with cavitation (Table 2). Within the subgroups randomised for immunotherapy, the REClari group had higher proportions with BCG vaccination, and who were female. In the trial population as a whole the distributions were similar for REClari and RECipro.

Deviations from protocol
In 140 patients the protocol was not followed: 75 (20.2%) experienced unwanted effects necessitating a change of the regimen, 38 (20.5%) RE Cipro and 37 (19.9%) REClari. Of these 75 patients, 54 received treatment different from that allocated because of unwanted effects definitely caused by a single drug - R 9 (2.4%), E 20 (5.4%), Cipro 17 (9.2%), Clari 8 (4.3%). A further 17 patients were intolerant to each (definitely or possibly) of the 3 drugs in their regimen (9 RECipro, 8 REClari) whilst 4 other patients (all RECipro) were intolerant of two (definitely or possibly) of their three drugs. Overall, Clari was associated with unwanted effects in 16 (8.6%), whereas Cipro was associated with unwanted effects in 29 (15.6%), Difference of -7.1%, 95% CI -13.7% to -0.5%, p = 0.05. The corresponding figures for R were 12 (6.5%) and 15 (8.1%), p = 0.68. Among the REClari patients there were 25 (13.4%) with unwanted effects attributed to ethambutol compared with 16 (8.6%) in the RECipro group (Difference of 4.8%, 95% CI -1.6% to 11.2%, p=0.19). Within these, visual problems predominated in the REClari patients (n = 15, 8.1%), compared with 5 (2.7%) in the RECipro group (Difference of 5.4%, 95% CI 0.8% to 9.9% p = 0.04). However on retrospective enquiry after the end of the trial it was discovered that in at least 4 of the 15 REClari patients and in 1 of the 5 RECipro patients, the visual problems had been attributed incorrectly to ethambutol, altering the comparison to REClari 11 vs RECipro 4 (Difference of 3.8%, 95% CI -0.2% to 7.7%, p=0.12).

In a further 62 patients treatment varied from that allocated because of physicians’ errors, general practitioners’ errors, other medical/surgical problems (none were HIV/AIDS) or patients’ non-compliance with treatment or follow-up: in all of these respects there were no differences between the REClari and RECipro groups, nor were there any differences between the groups randomized to M.vaccae or to no
M. vaccae. In addition, there were 3 patients, randomised to REClari, who were unable to tolerate Cipro when added as a 4th drug.

Immunotherapy

Considering the 170 patients who participated in the immunotherapy limb of the trial (Table 3), no significant differences were found within species, nor overall, between those receiving M. vaccae and those not, in terms of total deaths - M. vaccae 36 (42.9%), no M. vaccae 38 (44.2%), deaths due to opportunistic mycobacterial disease (M. vaccae 5 (6%), no M. vaccae 2 (2.3%), failure of treatment (M. vaccae 6 (7.1%), no M. vaccae 3 (3.5%) and relapses (M. vaccae 2 (2.4%), no M. vaccae 4 (4.7%). A poor outcome of treatment (death due to opportunistic mycobacterial disease or failure of treatment or relapse) was experienced by 13 (15.5%) in the M. vaccae group and 8 (9.3%) in the no M. vaccae group (difference 6.2%, 95% CI -3.7%, 16.0%, p = 0.32).

For purposes of the comparison of REClari with RECipro these 170 patients were therefore combined with the 201 who had opted not to enter the immunotherapy limb, giving totals for analysis of 186 in the REClari group and 185 in the RECipro group.

Comparisons of the chemotherapy regimens (n=371)

Deaths

Within each species and overall, the number of patients who died because of mycobacterial disease did not differ between the REClari and RECipro treatment groups: REClari 6 (3.2%), RECipro 6 (3.2%), Table 4

In the total trial population there was no difference in all-cause mortality between the REClari and RECipro regimens (Mantel-Haenszel $\chi^2 < 0.001$, p = 0.99), but there was
significant heterogeneity in the magnitude of the treatment effect across the three species (Breslow-Day Test of homogeneity of odds ratios: p = 0.006), Table 4: among the MAC patients, the mortality was higher in the Clari arm (48% vs 29%), whilst this was reversed for the patients with *M. malmoense* (42% vs 56%) and *M. xenopi* (29% vs 47%).

Of the 148 patients who died from causes other than mycobacterial disease, 58 died of respiratory failure, 17 of lung cancer, 2 of pneumonia, 1 of pneumothorax, 1 of cor pulmonale, 1 of pulmonary embolism, 28 of other cardiovascular diseases, 14 of non-respiratory malignancy and 9 of other causes (none due to AIDS or drug toxicity). In relation to these various causes of death, there were no differences between the REClari and RECipro regimens. In 17 patients (9 REClari, 8 RECipro) the cause of death was uncertain.

Failures of treatment and relapses
Among the REClari patients 19 (10.2%) either failed treatment (n=7) or relapsed after the end of treatment (n=12), compared with 25 (13.5%) in the RECipro group (18 failures of treatment and 7 relapses), Difference of -3.3%, 95% CI -9.9% to 3.3%, p=0.41 (Table 4).

Poor outcome
Combining death due to mycobacterial disease with failure of treatment and relapse to generate the index ‘poor outcome’, there was no evidence of an overall treatment effect of REClari versus RECipro (Mantel-Haenszel $\chi^2 = 0.72$  p = 0.40), nor was there evidence of different treatment effects in the three species (Breslow-Day Test: p
Poor outcome rates did differ between the species (MAC 19%; *M.xenopi* 18%; *M.malmoense* 7%; $\chi^2 = 11.1, p = 0.004$). The overall poor outcome rate of Cipro was 15.7%, compared with 11.8% on Clari (Difference 3.8%; 95% CI, -3.2%, 10.8%, p=0.21).

Good outcome

The differences between REClari and RECipro in terms of those patients classified as “completing treatment as allocated, alive and cured at 5 years” were significant at the 5% level overall: RE Clari 56 (30.1%), RE Cipro 38 (20.5%), diff. 9.7%, CI 0.9%, 18.5%, p=0.04 (Table 4). This difference was only observed in those with *M.malmoense* (Clari 38.4%, Cipro 19.8%), with almost identical results for the other two species, but this apparent species by treatment interaction was not statistically significant (Breslow-Day Test: p = 0.23). Taking those patients who, regardless of deviations from allocated treatment, were deemed to be “alive and cured at 5 years” (REClari 74 (40%) and RECipro 61 (33%), see Table 4), the same pattern of differences was apparent, although not statistically significant (Difference of 6.8%, CI -3.0%, 16.6%, p=0.21).

Clinical progress and other indices of outcome

Clinical progress: overall this was recorded on 856 occasions during the trial. Poor progress was noted on 141 (16.5%) of these, 54 of which were attributed to the mycobacterial disease (6% of all recordings, 38% of poor progress recordings). There was no statistically significant difference between REClari and RECipro in the proportions with poor progress at every time-point throughout follow-up.
**Fourth drug:** among the 32 patients (REClari 13, RECipro 19) requiring a fourth drug at the end of their first year of treatment, 4 (13%) died from mycobacterial disease compared with 2 of 219 (1%) who had not required a fourth drug ($\chi^2 = 11.5$, $p=0.001$). No difference was found in all-cause mortality between those requiring the fourth drug and those in whom it was not deemed necessary.

**Weight changes:** 38% of those who relapsed ($n = 16$) had lost 3 kg or more at the time of their relapse compared with 25% of those cured at 5 years ($n = 91$). Of those cured, 51% had gained 3 kg or more compared with 13% of those who had relapsed ($\chi^2_{\text{trend}} = 5.0$, $p = 0.03$). A comparison of these groups based on weight changes at the end of their 2 years of treatment showed a similar pattern ($\chi^2_{\text{trend}} = 4.0$, $p = 0.046$).
Discussion

In the tradition of randomised controlled trials conducted by the British Thoracic Society, this study was set up to compare two promising antibiotic drugs in the context of chemotherapy for the treatment of opportunistic mycobacterial infections and to gather evidence of the benefit of immunotherapy with *M.vaccae*. The likely level of recruitment to the trial was unknown but the sub-committee planning the study took the view that it was preferable to collect data from a randomised, prospective comparison than to collect observational data, or no data at all. It is debatable whether such a view would be acceptable to a modern Ethics Committee, but the result was the largest ever, randomised trial investigating the treatment of pulmonary disease due to MAC, *M.Malmoense* or *M.Xenopi* in the setting of routine NHS Chest Clinics.

Immunotherapy with four doses of *M.vaccae* over the first six months of chemotherapy did not improve the outcomes of either chemotherapy regimen, or overall outcome. Initially a promising modality of treatment with which to supplement chemotherapy for mycobacterial disease\(^{12-15}\), immunotherapy with *M.vaccae* has not fulfilled expectations when used in the treatment of tuberculosis \(^{16-19}\). The same disappointing results has now been demonstrated in a large, prospective trial of treatments for pulmonary disease caused by MAC, *M.malmoense* and *M.xenopi*. It is possible that shorter intervals between doses of *M.vaccae* and/or administration for longer might have produced different results but, as things stand currently, immunotherapy with *M.vaccae* cannot be recommended as part of the treatment of patients with lung disease caused by MAC, *M.malmoense* and *M.xenopi*. 

16
Over the three species combined, REClari and RECipro did not differ meaningfully in terms of deaths due to mycobacteria, failures of treatment + relapses and deaths due to all causes. More patients on REClari (30.1%) completed treatment as allocated and were alive and cured at the end of five years than did those on RECipro (20.5%), $p = 0.04$: this effect stemmed from the results in patients with *M. malmoense* and was not evident for those with MAC or *M. xenopi*. In the previous BTS study of the treatment of MAC, *M. malmoense* and *M. xenopi*, it was shown that there was no correlation between clinical outcome and the results of susceptibility tests to the antimycobacterial drugs R, H and E when tested singly in vitro\(^1\). In laboratory studies the combination of R and E has been found to act synergistically in vitro against opportunist mycobacteria\(^{20-22}\) and in the first BTS study this combination (+/-H) resulted in outcomes better than those achieved by earlier 5- or 6-drug regimens\(^1\)\(^{23-28}\). It was hoped that triple drug regimens containing Clari and Cipro, in combination with RE, might prove more effective than RE or REH had been, but this does not appear to be the case (Table 5).

With the regimens used in this trial the frequency of unwanted effects leading to a change of treatment were twice that encountered with RE and REH\(^1\). Although the REClari and RECipro groups were little different from each other in this respect, but in the REClari group there was a trend for more patients to experience unacceptable, unwanted effects attributed to E than was the case for the RECipro group, especially visual problems. The protocol did not require ophthalmological opinion or measurement of E levels for patients with visual problems but enquiry after the end of the trial indicated that not all of these visual problems were truly ethambutol-related. Adjustment of the figures to take account of this information resulted in loss of
statistical significance of the difference between REClari and RECipro. Physicians using ethambutol in the treatment of mycobacterial disease are very aware of its potential effects on the eyes and perhaps tend to err on the side of caution, stopping ethambutol unnecessarily in some instances.

Mortality rates at 5 years were over 40%, as they had been in the earlier trial, the majority dying from causes other than the mycobacterial disease. Deaths attributed to opportunistic mycobacterial disease were uncommon but were more frequent in those who still had sputum which was culture-positive for mycobacteria at 12 months. Until new drugs are developed which can supplement those currently available for treating the patients with these diseases, physicians are left with the common sense measure of improving general health and optimising treatment of concomitant diseases as the only other options with potential for further reducing mortality and morbidity, focusing particularly on those not doing well at 12 months.

The BTS Guidelines for the treatment of these conditions recommended RE as a regimen which improved outcome when compared with no treatment or treatment which included 4, 5 or 6 drugs chosen on the basis of in vitro susceptibility tests. Table 5 shows the outcomes for each species with each of four regimens (RE and REH from the previous study and REClari and RECipro from the current study). Comparisons of these outcomes can only be cautiously interpreted as they are derived from different trials and, in deciding on which regimen to choose initially, account should be taken of the increased incidence of unwanted effects with the Clari or Cipro regimens. For MAC, REClari was associated with an all-causes death rate higher than with any other regimen whereas more patients had “good outcome” with REH.
However, the death rate due to mycobacterial disease was higher with REH than with RE. Perhaps the “best-buy” initial regimen could be RE, adding H or Cipro if the patient is not doing well at 12 months. For *M. malmoense* the “all-causes death rate” with RECipro was higher than with the other regimens. There appears to be little to choose between RE, REH and REClari in terms of efficacy but unwanted effects were more frequent with REClari. For *M. xenopi* REClari appears best in terms of efficacy but would be likely to carry more risk of unwanted effects than RE.

This largest-ever, randomised trial, performed in the setting of routine chest clinics, has provided further evidence to guide clinicians managing these conditions. However, the outlook for patients with pulmonary disease due to MAC, *M. malmoense* or *M. xenopi* treated with currently available drugs continues to be poor. As these diseases appear to be markers of poor health, studies of various methods of optimising general health and of managing co-morbidity in this population are needed, just as much as research into better antmycobacterial drugs with which to devise new regimens for testing in clinical trials.
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Although representatives of their Medical Departments agreed the protocol, they played no part in the experimental design, data collection, analysis and production of the report.

CONTRIBUTORS

The first draft of the protocol was written by Dr. Campbell and modified after discussion by the sub-committee. Data entry was overseen by Dr. Campbell. Professor Prescott supervised data checking and performed the statistical analyses. The first draft of the report was produced by Dr. Campbell, who made amendments in the light of discussion and comment by the sub-committee. The penultimate draft was scrutinised by the Research Committee and the final version then prepared by Dr. Campbell.

CONFLICTS OF INTEREST

None arose.

STATEMENT

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References


Table 1
Pre-treatment characteristics of patients not opting for the immunotherapy limb

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th>M.malmoense</th>
<th>M.xenopi</th>
<th>All 3 species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REClari (n=47)</td>
<td>RECipro (n=50)</td>
<td>REClari (n=43)</td>
<td>RECipro (n=40)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>25 / 22</td>
<td>20 / 30</td>
<td>30 / 13</td>
<td>24 / 16</td>
</tr>
<tr>
<td>Mean Age (yrs) (SD)</td>
<td>67.3 (11.6)</td>
<td>64.6 (12.5)</td>
<td>62.7 (11.4)</td>
<td>62.7 (12.3)</td>
</tr>
<tr>
<td>BCG vaccination</td>
<td>7 (15%)</td>
<td>9 (18%)</td>
<td>3 (7%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Cavitation</td>
<td>33 (70%)</td>
<td>32 (64%)</td>
<td>17 (40%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>&gt;= 3 zones</td>
<td>8 (17%)</td>
<td>5 (10%)</td>
<td>9 (21%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Other pulmonary disease on chest radiograph</td>
<td>29 (62%)</td>
<td>26 (52%)</td>
<td>8 (19%)</td>
<td>16 (40%)</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th></th>
<th>M.avium intracellulare RE</th>
<th>M.malmoense RE</th>
<th>M.xenopi RE</th>
<th>All three species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M.vaccae Clari (n=17)</td>
<td>No M.vaccae Clari (n=19)</td>
<td>M.vaccae Clari (n=21)</td>
<td>No M.vaccae Clari (n=22)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/11</td>
<td>13/6</td>
<td>9/10</td>
<td>11/7</td>
</tr>
<tr>
<td>Mean Age (yrs) (SD)</td>
<td>64.1 (13.2)</td>
<td>63.8 (11.2)</td>
<td>62.1 (9.9)</td>
<td>66.3 (9.6)</td>
</tr>
<tr>
<td>BCG vaccination</td>
<td>5 (29%)</td>
<td>3 (16%)</td>
<td>5 (26%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Cavitation</td>
<td>14 (82%)</td>
<td>12 (63%)</td>
<td>10 (53%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>&gt;= 3 zones</td>
<td>2 (12%)</td>
<td>6 (32%)</td>
<td>7 (37%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Other pulmonary disease on chest radiograph</td>
<td>8 (47%)</td>
<td>10 (53%)</td>
<td>9 (47%)</td>
<td>10 (56%)</td>
</tr>
</tbody>
</table>
Table 3
Results during and after treatment among those entering the immunotherapy randomisation.

<table>
<thead>
<tr>
<th></th>
<th>M. avium intracellulare</th>
<th>M. malmoense</th>
<th>M. xenopi</th>
<th>All 3 species</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 3</td>
<td>RE</td>
<td>RE</td>
<td>RE</td>
<td>RE</td>
</tr>
<tr>
<td>M. vaccae</td>
<td>No M. vaccae</td>
<td>M. vaccae</td>
<td>No M. vaccae</td>
<td>M. vaccae</td>
</tr>
<tr>
<td>Clari</td>
<td>Cipro</td>
<td>Clari</td>
<td>Cipro</td>
<td>Clari</td>
</tr>
<tr>
<td>Number entered</td>
<td>17</td>
<td>19</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Number deviated *</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4th drug required (added)</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Deaths due to Mycob. disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Failures of treatment</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapses</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>No. completed treatment as</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Notes:
- RE: Response Effective
- Mv: M. vaccae
- no Mv: No M. vaccae
- *: Number deviated
- 11D: One patient died during treatment

**Summary**

- Among those entering the immunotherapy randomisation, the results showed varying outcomes based on the species and additional treatments required.
- The number of deaths varied across species, with the highest number of deaths observed in the category of deaths due to Mycob. disease.
- Failures of treatment and relapses were also recorded, indicating the challenges in achieving successful treatment outcomes.

**Data Analysis**

- The number of patients entering treatment ranged from 17 to 84 across different species and treatment combinations.
- The number of patients deviating from the treatment protocol ranged from 6 to 9, indicating the need for close monitoring and possible adjustments in treatment regimens.
- The use of the 4th drug was varied across species, with some requiring it in a significant proportion.
- Deaths from all causes showed a range from 1 to 17, with M. xenopi having the highest number of deaths among all species.
- Failures of treatment and relapses were also noted, highlighting the need for robust follow-up and care.
| No. alive and cured at 5 years | 8 (47%) | 5 (26%) | 6 (32%) | 7 (39%) | 10 (48%) | 5 (24%) | 13 (59%) | 4 (20%) | 1 (50%) | 1 (25%) | 2 (50%) | 2 (67%) | 19 (48%) | 11 (25%) | 21 (47%) | 13 (32%) | 30 (36%) |
|--------------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|

D - Death due to Mycob. disease  
* Reasons for deviation are detailed in the second section of Results.
Table 4
Results for all patients during and after treatment

<table>
<thead>
<tr>
<th></th>
<th>All Clari (186)</th>
<th>All Cipro (185)</th>
<th>All (371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MAC</td>
<td>M.mal</td>
<td>M.xen</td>
</tr>
<tr>
<td>Number entered</td>
<td>83</td>
<td>86</td>
<td>17</td>
</tr>
<tr>
<td>Number deviated *</td>
<td>29 (35%)</td>
<td>21 (24%)</td>
<td>10 (59%)</td>
</tr>
<tr>
<td>4th drug required (added)</td>
<td>10 (10)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>40 (48%)</td>
<td>36 (42%)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Deaths due to Mycob. disease</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Failures of treatment</td>
<td>41D</td>
<td>11D</td>
<td>2</td>
</tr>
<tr>
<td>Relapses</td>
<td>7</td>
<td>31D</td>
<td>2</td>
</tr>
<tr>
<td>No. completed treatment as allocated and alive and cured at 5 years</td>
<td>20 (24%)</td>
<td>33 (38%)</td>
<td>3 (18%)</td>
</tr>
<tr>
<td>No. alive and cured at 5 years</td>
<td>26 (31%)</td>
<td>42 (49%)</td>
<td>6 (35%)</td>
</tr>
</tbody>
</table>
D - Death due to Mycob. disease * Reasons for deviation are detailed in the second section of Results.
Table 5
Comparative outcomes of four regimens in the treatment of lung diseases caused by MAC, M.malmoense and M.xenopi

<table>
<thead>
<tr>
<th></th>
<th>MAC</th>
<th>M.malmoense</th>
<th>M.xenopi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RE</td>
<td>REH</td>
<td>REClari</td>
</tr>
<tr>
<td>No. patients</td>
<td>37</td>
<td>38</td>
<td>83</td>
</tr>
<tr>
<td>Deviated from protocol</td>
<td>16%</td>
<td>21%</td>
<td>35%</td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>32%</td>
<td>39%</td>
<td>48%</td>
</tr>
<tr>
<td>Deaths (due to Mycobacteria)</td>
<td>0%</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Failures of treatment and relapses</td>
<td>41%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Completed treatment as allocated, alive &amp; cured at 5 years</td>
<td>27%</td>
<td>34%</td>
<td>24%</td>
</tr>
</tbody>
</table>

NB: percentages do not always add up to 100% because some patients who died had earlier been failures of treatment or relapses.
## Supplemental online table

95% Confidence Interval and Associated p-values for comparison of Clari and Cipro (Clari – Cipro) within the three species.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAIS Clari (83)</th>
<th>Cipro (87)</th>
<th>p-value</th>
<th>MAIS Clari (86)</th>
<th>Cipro (81)</th>
<th>p-value</th>
<th>MAIS Clari (17)</th>
<th>Cipro (17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>18.3</td>
<td>3.9, 32.7</td>
<td>0.02</td>
<td>-13.7</td>
<td>-28.7, 1.3</td>
<td>0.11</td>
<td>-17.6</td>
<td>-49.8, 14.5</td>
<td>0.48</td>
</tr>
<tr>
<td>Death due to mycobacteria</td>
<td>-1.0</td>
<td>-6.1, 4.0</td>
<td>1.0</td>
<td>2.2</td>
<td>-3.4, 7.8</td>
<td>0.73</td>
<td>-5.9</td>
<td>-17.1, 5.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>19.3</td>
<td>5.2, 33.5</td>
<td>0.01</td>
<td>-15.9</td>
<td>-30.8, -1.0</td>
<td>0.04</td>
<td>-11.8</td>
<td>-43.6, 20.1</td>
<td>0.72</td>
</tr>
<tr>
<td>Failure of treatment or relapse</td>
<td>-9.7</td>
<td>-21.2, 1.7</td>
<td>0.15</td>
<td>-0.3</td>
<td>-6.8, 6.2</td>
<td>1.0</td>
<td>17.6</td>
<td>-5.4, 40.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Poor outcome (death due to mycob or failure or relapse)</td>
<td>-9.7</td>
<td>-21.4, 2.1</td>
<td>0.16</td>
<td>-0.4</td>
<td>-8.3, 7.4</td>
<td>1.0</td>
<td>11.8</td>
<td>-13.6, 37.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Good outcome (completed treatment as allocated, alive and cured at 5 years)</td>
<td>1.1</td>
<td>-11.7, 13.9</td>
<td>1.0</td>
<td>18.6</td>
<td>5.2, 32.1</td>
<td>0.01</td>
<td>5.9</td>
<td>-17.8, 29.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>