Opportunistic mycobacterial lung disease – which drug combination is more effective?

The cornerstone of treatment for pulmonary disease caused by opportunistic mycobacteria is rifampicin and ethambutol. The role of macrolides, quinolones and immunotherapy with *Mycobacterium vaccae* remains unclear. The aim of this study was to compare clarithromycin (Clari) and ciprofloxacin (Cipro) as third drugs for pulmonary disease caused by *M. avium-intracellulare* (MAC), *M. malmoense* and *M. xenopi* (REClari and RECipro). Immunotherapy with *M. vaccae* versus no immunotherapy was also performed.

**Methods**

Patients were aged ≥16 years (all HIV negative) with clinical/radiological evidence of active mycobacterial disease. Sputum was positive on culture for MAC, *M. malmoense* or *M. xenopi* on ≥2 occasions. Four treatment regimens were used: 1) RECipro; 2) RECipro + *M. vaccae* 4 times in first 6 months; 3) REClari; and 4) REClari + *M. vaccae* 4 times in first 6 months. The dosages were: rifampicin 450 mg (or 600 mg in those weighing ≥50 kg) orally once daily, ethambutol 15 mg per kg orally once daily, ciprofloxacin 750 mg twice daily, *M. vaccae* 0.1 mL intradermally on entry and every 2 months up to 6 months (i.e. four doses in all). If sputum at 12 months proved positive on culture, the fourth drug (Cipro to those on REClari or Clari to those on RECipro) was added. At 24 months chemotherapy was discontinued. Patients whose sputum was still positive on culture on ≥2 occasions in the last 3 months of treatment, and those who despite treatment deteriorated as a result of mycobacterial disease, were classed as treatment failures. After a patient had completed chemotherapy, the physician was asked to report clinical and bacteriological status (two specimens of sputum) every year for a further 3 years (i.e. up to 5 years from entry to the trial). Those whose sputum became positive on culture were classed as relapses. If the patient died during the study, cause of death was classified as being caused either by opportunistic mycobacterial pulmonary disease or not.

**Results**

In total, 191 physicians from England, Scotland, Wales, Denmark, Finland, Norway, Sweden and Italy entered 371 patients for analysis (170 MAC, 167 *M. malmoense* and 34 *M. xenopi*). Of these, 201 opted not to enter the immunotherapy randomisation and were randomised just between REClari and RECipro. 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 received *M. vaccae* and chemotherapy while 86 received chemotherapy but no *M. vaccae*. The number of patients who died because of mycobacterial disease did not differ between the REClari and RECipro treatment groups (3.2%). One hundred and forty-eight patients who died from causes other than mycobacterial disease, 58 died of respiratory failure, 17 of lung cancer, two of pneumonia, one of pneumothorax, one of cor pulmonale, one of pulmonary embolism, 28 of other cardiovascular diseases, 14 of nonrespiratory malignancy and nine of other causes (none due to AIDS or drug toxicity). There were no differences between the REClari and RECipro regimens. In 17 patients (nine REClari and eight RECipro), the cause of death was uncertain. In the REClari group, 10.2% either failed treatment or relapsed compared with 13.5% in the RECipro group.

**Editorial comment**

This randomised controlled trial, which was conducted by the British Thoracic Society, is the largest ever randomised trial investigating the treatment of pulmonary disease due to MAC, *M. malmoense* or *M. xenopi*. Over the three species combined, different therapeutic regimens (REClari and RECipro), did not differ meaningfully in terms of deaths due to mycobacteria, failures of treatment, relapses and deaths due to all causes. Immunotherapy with four doses of *M. vaccae* over the first 6 months did not improve the outcome. Immunotherapy with *M. vaccae* has not fulfilled expectations when used in the treatment of tuberculosis. The same disappointing result has now been demonstrated in the treatment of pulmonary disease caused by opportunist mycobacteria. As these diseases appear to be markers of poor health, optimising general health, managing comorbidity in this population and research for better antitycobacterial drugs are needed urgently.

**References**


**Message**

There is no difference in treatment outcome when using clarithromycin versus ciprofloxacin as adjuncts to rifampicin and ethambutol in medical treatment of opportunistic mycobacterial lung diseases. Immunotherapy with *Mycobacterium vaccae* does not improve outcome.

**Competing interests**

None declared.