Non-Tuberculous Mycobacteria: Passengers or Pathogens?

S38 CLINICAL ISOLATES OF MYCOBACTERIUM AVIUM DRIVE COLLAGENOLYTIC AND ELASTOLYTIC ACTIVITY IN MONONUCLEAR CELLS

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Background Pulmonary non-tuberculous mycobacterial (NTM) infections are increasing rapidly in the UK. The commonest pulmonary NTM infection outside the setting of cystic fibrosis lung disease is with the mycobacterium avium complex (MAC), consisting of *M. avium* and *M. intracellulare*. Patients with pulmonary MAC infection present with cavitatory lung disease or nodular bronchiectasis. Prolonged treatment is required, frequently not tolerated, and often associated with progressive lung destruction. A large body of evidence suggests the tissue damage that occurs in tuberculous lung disease is driven by host derived matrix metalloproteinases (MMPs), in particular MMP-1 and 9. The mechanisms of tissue damage in NTM infection are not understood. We hypothesised that NTM drives MMP secretion and that this drives cavitation and bronchiectasis.

Methods Monocytes isolated from healthy human volunteer blood by density centrifugation were stimulated with *M. avium* clinical isolates for 24 hours. Human monocyte-derived macrophages (MDMs) were generated from monocytes through 5–7 day incubation with GM-CSF before stimulation with four different clinical isolates of *M. avium* for up to 72 hours. mRNA expression was investigated using qRT-PCR. Protein in cell supernatants was quantified using ELISA and Luminex array techniques.

Results Stimulation with *M. avium* does not increase MMP-9 secretion in monocytes or macrophages. *M. avium* significantly increases gene expression of MMP-1 and induces MMP-1 secretion by MDMs (Figure 1). Additionally, *M. avium* drives induction of MMP-7, an elastolytic enzyme (Figure 1), and reduces the secretion of TIMP-1; the major *in vivo* inhibitor of MMP-1.

Conclusions Interestingly, unlike *Mycobacterium tuberculosis* or other chronic pulmonary pathogens such as *Pseudomonas* or *Haemophilus influenzae*, *M. avium* does not drive secretion of MMP-9 by infected mononuclear cells from healthy donors. Instead it drives functionally unopposed MMP-1, which was previously thought to be an *M. tuberculosis*-specific response. Data suggest MMP-1 and −7 may drive the destructive pulmonary pathophysiology that characterises *M. avium* infection. This will be further investigated with patient sputum samples and inflammatory cells.

S39 RISK OF NTM (NON TUBERCULOUS MYCOBACTERIUM) INFECTION IN PATIENTS ON LONG TERM PROPHYLACTIC MACROLIDE ANTIBIOTICS

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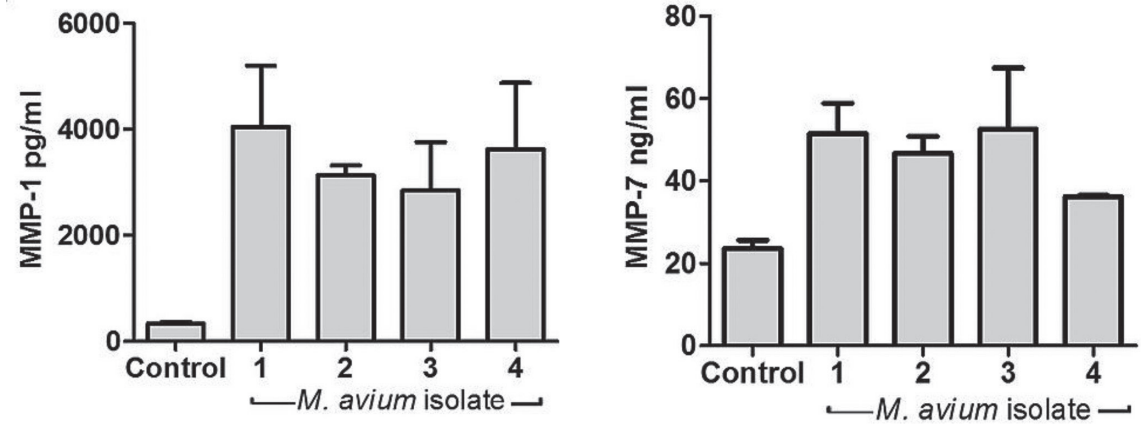
Introduction Long term prophylactic macrolide therapy is commonly used in respiratory diseases characterised by persistent airway inflammation and chronic bacterial infection. There is growing evidence that they possess immuno-regulatory and anti-inflammatory effects as well as an antimicrobial action. The development of macrolide resistant bacteria, particularly NTM infection, is a concern because macrolide therapy is the primary treatment of NTM. There is little published data investigating this risk.

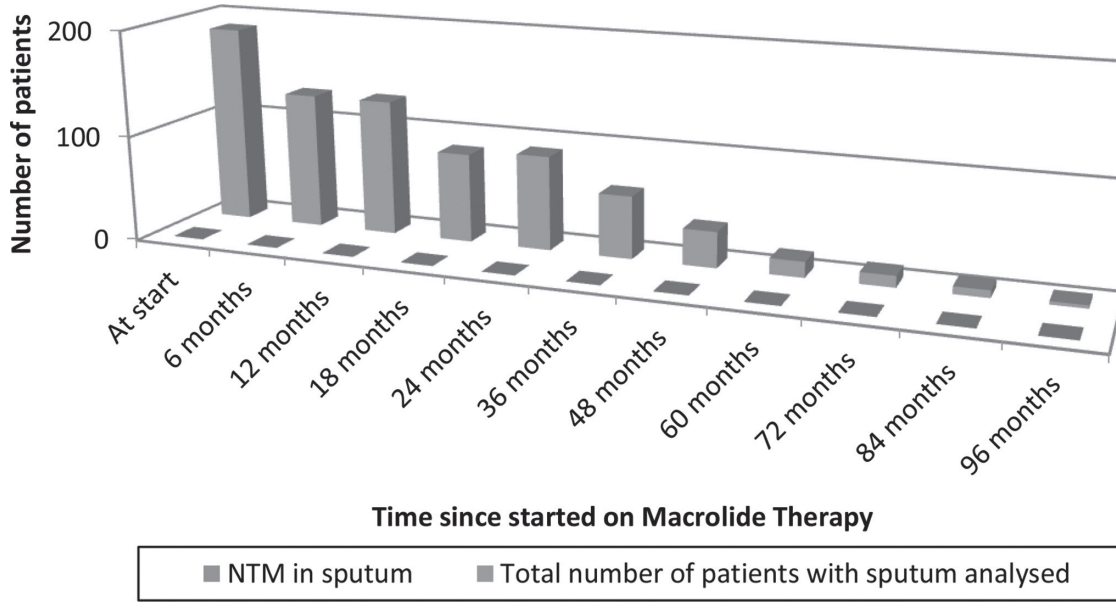
Methods We identified the cases, retrospectively, of all adult patients who had been given long term continuous prophylactic macrolide therapy attending the respiratory outpatients clinic until January 2016 at Russell Hall Hospital. The clinic letters were reviewed to get a clinical diagnosis and then data regarding sputum culture results were collected from the electronic reporting system. Approximately 75% of cases were reviewed.

Results 226 patient cases were reviewed. 192 (85%) were on long term Clarithromycin. 86 (38%) had a diagnosis of COPD; 133 (59%) of Non CF Bronchiectasis and 100 (44%) of Asthma. The average starting FEV1 was 1.55. The average change in FEV1 was −0.1 (range −3.22 to +1.07). Average time on macrolides was 3 years and 10 months (range 11 months to 8 years and 8 months). Out of all those who had sputum analysed, not one patient demonstrated evidence of NTM infection in their sputum up to 96 months (Figure 1).

Conclusion Our data suggests that the use of long term prophylactic macrolide therapy in the treatment of respiratory disease does not increase the risk of NTM infection and therefore should not be a concern to limit use in clinical practice. However



Abstract S38 Figure 1 MMP-1 (left) and MMP-7 (right) secretion from MDMs at 72 hours post stimulation with 4 different clinical isolates of *M. avium*



Abstract S39 Figure 1 NTM infection in sputum of patients on long term macrolides

randomised controlled trials involving larger populations of patients are required to confirm the benefits and harms.

S40 A RETROSPECTIVE STUDY INTO THE CLINICAL RELEVANCE OF ISOLATING NON-TUBERCULOUS MYCOBACTERIA IN PULMONARY SAMPLES

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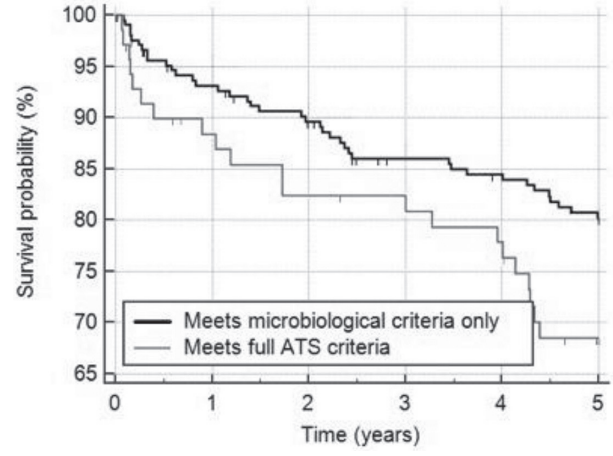
Introduction and objectives There are in excess of 160 species of non-tuberculous mycobacteria (NTM), the minority of which can cause infection predominantly in patients with an underlying respiratory disease such as bronchiectasis or cystic fibrosis. Isolation of NTM in the respiratory tract does not always signify infection and can represent a transient infection, colonisation or active infection. The American Thoracic Society (ATS) criteria for the diagnosis of NTM infection can be used to help assess clinical relevance and the need to treat patients. A retrospective study was conducted to assess the clinical relevance of different species of NTM isolation.

Methods A database of microbiology results at a specialist trust was reviewed for patients with positive NTM isolates between January 2005 and December 2010. These patients were assessed against the ATS diagnostic criteria of NTM lung disease. Patient records for those who met the microbiological criteria records were reviewed for demographics, underlying condition and course of infection. Patients were followed up for a minimum of 5 years, or until discharge/death.

Results Five hundred and fifty-five (555) patients with positive NTM cultures were found, 281 (51%) of whom met the ATS microbiological criteria. 70 (13%) patients met the radiographic criteria and so were likely to have an active infection. This varied by species: *M. Avium Complex (MAC)* (21%), *M. malmoense* (20%), *M. abscessus* (18%) and *M. kansasii* (17%) were most likely to cause changes on CT, and species such as *M. fortuitum* (1.6%) and *M. gordonae* (0%) were less likely. The proportion of patients treated also varied by species, with *M. abscessus* (45%), *M. kansasii* (23%) and *MAC* (20%) most likely to be treated. Five-year mortality for all patients who met the microbiological criteria was 21.4% and was significantly associated with meeting the full ATS criteria, as shown by Figure 1. Five-year survival and the patient's underlying condition also varied by species.

Conclusions Clinical relevance of NTM isolation varies by species, clinical symptoms and underlying condition. The decision to treat is influenced by these factors in addition to the ATS criteria.



Abstract S40 Figure 1 5-year survival of patients who meet full ATS criteria versus thode who only meet microbiological criteria N = 281 (p = 0.041)