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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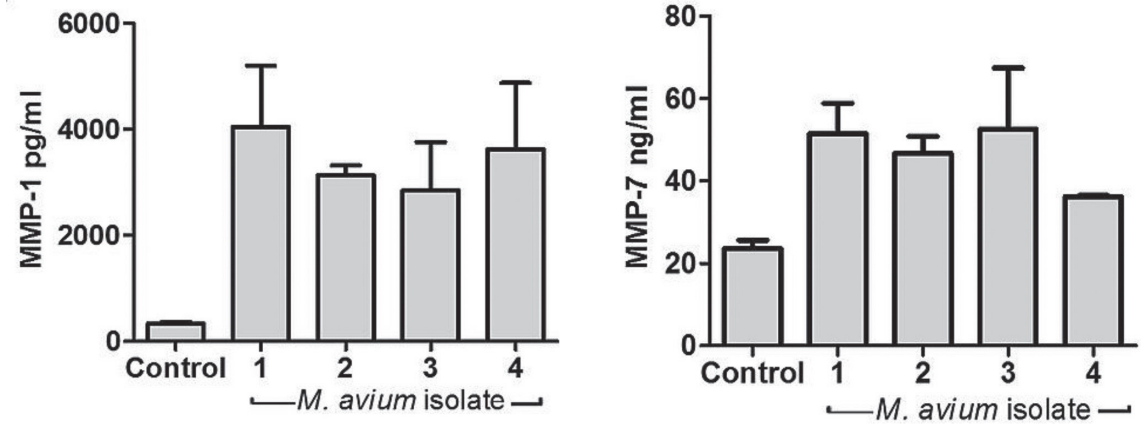
Introduction Long term prophylactic macrolide therapy is commonly used in respiratory diseases characterised by persistent airway inflammation and chronic bacterial infection. There is growing evidence that they possess immuno-regulatory and anti-inflammatory effects as well as an antimicrobial action. 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*