OP 08 - Blood analytes as biomarkers of disease severity and treatment response in tuberculosis

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Introduction: In tuberculosis, adequate powering of studies, and lengthy follow up times are required to reliably predict long term unfavourable outcomes, which is expensive and logistically challenging. Biomarkers of disease severity and surrogate markers of long-term outcomes are desirable.

Methods: A panel of 39 markers of inflammation, immune activation, tissue remodelling, and oxidative damage was measured in plasma of patients with tuberculosis undergoing anti-tuberculosis treatment (ATT) at Ubuntu Clinic, Khayelitsha, South Africa using Luminex-based multiplex assays. Samples were collected at baseline, 8 and 20 weeks of ATT. A multivariable logistic regression model was developed using analytes which were associated with a significantly ($p<0.05$) increased odds of unsuccessful treatment outcome (death/failure/recurrence), with adjustment for potential confounders.

Results: In a cohort of 130 patients (58% HIV co-infected), we found significant differences in the majority of blood analytes over the course of treatment. The neutrophil-associated metalloproteinases (MMP-9 and MMP-8) were positively correlated with IFNα2, IL-17 and IL-1β and negatively correlated with IL-1α. We found an association between Type 1 interferon response, neutrophil-associated cytokines and MMPs, and the presence of cavitatory disease. This was significantly influenced by HIV viraemia and HIV-associated immunosuppression. On multivariate analyses, Receptor Operator Curve-derived thresholds for IL-8, IL-6, MMP-3 and IL-1RA were used to predict unsuccessful treatment response both at baseline and 2 months.

Conclusions: These immune correlates suggest the IFN-inducible monocyte/neutrophil-driven response which has been linked with radiological disease severity may be mediated via up-regulation of gelatinase B (MMP-9) and collagenase-2 (MMP-8). IL-1α may be protective in this pathway. HIV viraemia and immunosuppression play a key role in modulating the inflammatory profile during ATT. Further studies will enhance understanding of spatio-temporal interactions at the site of disease, clinical phenotypes and elucidate downstream molecular mechanisms. Potential biomarkers predicting long-term outcomes identified should be validated further.

Key words: HIV-Tuberculosis co-infection; immune correlates; disease severity; biomarkers

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