Diagnostics and biomarkers

OC - (8711) - EARLY BIOMARKERS OF LUNG INFLAMMATION AND FUNCTION IN TRIALS OF HOST-DIRECTED TUBERCULOSIS THERAPIES (TB-HDT)

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**Background:** Permanent lung injury and impaired function are common despite TB cure. Host-directed anti-inflammatory therapies may prevent this injury. Early biomarkers of lung inflammation and function can facilitate their evaluation.

**Methods:** In an ongoing study supported by the Bill and Melinda Gates foundation, HIV-uninfected patients with radiographically moderately or far advanced sputum smear positive pulmonary tuberculosis receive rifabutin-substituted standard therapy plus either CC-11050 (phosphodiesterase inhibitor), everolimus (mTOR inhibitor), auranofin (gold salt), cholecalciferol, or control, during months 1-4. Study leadership is blinded to assigned treatments. 18F-fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT) are performed at baseline and at week 8. Total lung glycolytic activity (SUVbw*ml) and radiodensity (modified HU*ml) are measured using MIM software. Sputum culture, spirometry, 6 minute walk test (6MWT), and other biomarkers are performed at multiple time points. Follow-up continues to month 18. This analysis includes only baseline and week 8 data.

**Results:** 160/200 participants are presently enrolled. At baseline, patients have a high burden of infection (median time to detection [TTD] in automated liquid culture 5 days). Median baseline FEV1% of predicted (63%) and 6MWT (402 meters) are typical of moderate to severe chronic lung disease. Baseline TTD, PET, CT, FEV1% and 6MWT are all highly correlated (median rank test P=.0018). All 5 parameters changed significantly during 8 weeks of treatment (P<.001). Analysis of adjusted log change from baseline shows PET and CT remain highly correlated (P<.001), and weakly correlated with FEV1% and 6MWT. TTD shows no correlation with any other endpoint.

**Conclusions:** Quantitative markers of infection, inflammation, and function are markedly abnormal and highly correlated at baseline in patients with pulmonary tuberculosis. Quantitative CT may substitute for PET as a more readily-performed measure of lung inflammation. The dissociation of microbiologic responses from inflammation and function supports a role for HDTs in TB.