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Ralph, Anna 2010 Pulmonary Tuberculosis: towards improved adjunctive therapies, PhD Dissertation, Menzies School of Health Research, The Australian National University. [fieldsite Timika and environs]

Abstract

The potential to improve pulmonary tuberculosis (PTB) treatment outcomes with adjunctive immunotherapies requires investigation. L-arginine and vitamin D have antimycobacterial properties which render them suitable candidates. Therefore the Arginine and Vitamin D Adjunctive therapy in Pulmonary TB (AVDAPT) trial evaluates these supplements in PTB. This large trial commenced in June 2008. The project is run in Timika, Papua Province, Indonesia by the International Health Division, Menzies School of Health Research (Darwin, Australia), the National Institute for Health Research and Development (Ministry of Health, Indonesia), and the Australian National University (Canberra).

Aims of this thesis were to design and commence the AVDAPT study and examine preliminary data. Among the tested hypotheses were that exhaled nitric oxide (FE_{NO}), an L-arginine-derived antimycobacterial immunological mediator, would be elevated in PTB compared with healthy controls (HC), and inversely related to disease severity; secondly, that significant relationships would exist between different measures of TB severity.

Consenting, eligible adults with smear-positive PTB were enrolled at the Timika TB clinic according to the protocol. Assessments included sputum microscopy, culture and susceptibility, X-ray, weight, pulmonary function, FE_{NO} , 6-minute walk testing (6MWT) and quality of life (St George's Respiratory Questionnaire [SGRQ]). HC were enrolled for a single assessment.

Results from 162 TB patients and 40 HC included: (1) findings pertaining to the trial (development / validation of outcome measures, and establishment of locally-relevant reference ranges for 6MWT and SGRQ); (2) findings pertaining to improved understanding of TB (demonstration of relationships between clinical, physiological,

immunological [FE_{NO}] and functional measures of disease severity), and (3) investigation of TB drug-resistance and HIV rates.

A key finding was that FE_{NO} was not elevated in TB compared with HC and was lower still in worse disease. These findings suggest that an impaired ability to generate adequate NO (e.g. in L-arginine deficiency) might contribute to host inability to adequately contain TB or mitigate lung pathology. These findings support the rationale for conducting a trial of adjunctive L-arginine in TB.

New relationships were identified between sputum smear grade, X-ray, weight, pulmonary function, 6MWT and SGRQ. Patients with more-severe malnutrition had worse pulmonary function; 6MWT was independent of lung function; SGRQ results accurately captured people's perceived quality of life, correlating significantly with symptoms, 6MWT and pulmonary function; and sputum bacillary grade was significantly related to radiological extent and weight, but not to other results. These findings support the use of a range of outcome measures in TB trials, to provide a comprehensive assessment of TB severity, rather than focusing on bacteriology alone.

An x-ray severity score and a clinical outcome score were created, providing valuable tools for use in clinical trials. Interim analysis confirmed the safety of L-arginine and vitamin D adjunctive therapy. Multi-drug resistant TB rates remained low in new cases (2.0%), but HIV-TB co-infection rates rose significantly over 5 years, creating major challenges.

This thesis provides the basis for continuation of the AVDAPT study, produces original findings relating to clinico-immunological aspects of PTB, and provides information of major local importance to help guide TB service provision in Timika.