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A leap forward in assessing host-directed therapies for tuberculosis

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With advances in diagnostic accuracy and therapeutic efficacy, 85% of people with pulmonary tuberculosis are successfully treated.[1] Despite favourable microbiological outcomes, long-term sequelae are common, including lung scarring leading to reduced pulmonary function and chronic respiratory symptoms.[2,3] Certain pulmonary function tests, such as FEV_1, correlate with long-term mortality,[4] yet few tuberculosis treatment trials have included lung function as a primary efficacy outcome.[5] Host-directed therapy, administered concurrently with standard tuberculosis therapy, could mitigate inflammation contributing to lung damage.[6]

We do not yet know which host-directed agents provide benefit for patients with tuberculosis, and there is no clear consensus on appropriate biomarkers, study endpoints, or agent selection criteria for trials investigating these therapies.[7] In a phase 2 trial reported in *The Lancet Respiratory Medicine*, Robert S Wallis and colleagues[8] evaluated the safety and efficacy of four candidate host-directed therapies (CC-11050, everolimus, auranofin, and ergocalciferol) plus rifabutin-substituted standard tuberculosis therapy compared with standard therapy alone.[8] Rifabutin was substituted for rifampicin to avoid drug interactions with everolimus and CC-11050. This trial recruited patients with a high baseline bacillary load and moderately advanced or far advanced radiographic disease. Such individuals have poor outcomes and might have the most to gain from effective host-directed therapies if, in fact, damage is—at least in part—reversible.[9]

Compared with control, CC-11050 and everolimus significantly increased FEV_1 (as a percentage of predicted) at day 180 (6·30%, 95% CI 0·06–12·54; p=0·048; and 6·56%, 0·18–12·95; p=0·044). Although a 6% increase in FEV_1 might seem modest, it is equivalent to an increase of 200 mL and is considerably higher than the difference deemed clinically relevant in trials of chronic obstructive pulmonary disease.[10] Auranofin and ergocalciferol did not show benefit. Furthermore, auranofin was associated with two treatment-attributable serious adverse events, comprising one death (due to intra-abdominal sepsis) and thrombocytopenia; episodes of syncope and acute hepatitis B were also seen in auranofin recipients, and the only treatment failure was in this group. These findings suggest that the risks outweigh the benefits for auranofin.

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This bold and ambitious study was novel because investigators compared multiple promising candidates and also explored relevant efficacy endpoints, including change in FEV_1 and sputum culture conversion; potential biomarker endpoints, such as ^{18}F-fluorodeoxyglucose-PET and CT changes, serum neopterin, QuantiFERON gold, gene expression profiles, and PD-1 expression, were also investigated (to be reported separately).

This study has some limitations.[8] Despite randomisation, there was an imbalance in the baseline FEV_1 and the extent of cavitary disease. The apparent FEV_1 gains at day 180 were not observed at day 540, a result that might be explained by the reduced sample size at this timepoint. Given these observations, correlating objective measures like FEV_1 with well validated, subjective, patient-centred outcomes, such as dyspnoea and quality of life, would be helpful.[10] Because there was not a dose-ranging component and samples were not collected for pharmacokinetic analysis, the selected doses, even for the two agents showing benefit, might not have been optimal for the indication. However, even if dosing is adjusted in future trials, these results provide early proof-of-concept data to guide later drug and endpoint selection.

Appropriate measures of pharmacodynamics for host-directed therapies have not yet been defined, although this trial collected data on several potential pharmacodynamic measures. As the field advances, it will be crucial to collect samples for pharmacokinetic and mechanism-specific biomarkers and clinical outcomes to link these three components and inform further candidate development. Also, given the immune system's contribution to both microbiological cure and inflammation, studying the performance of host-directed agents among patients with conditions that have immune system effects, such as EHIV and diabetes, will be important.

This trial was small, but groundbreaking in that it shows the potential benefit on lung function of two promising host-directed therapies and builds the knowledge and framework to support future trials of host-directed therapies for tuberculosis through its evaluation of relevant endpoints. This trial also highlights the fact that not all candidates are created equal; although many drugs have theoretical benefit, immune effects will be highly variable, and comparative risks differ considerably. Almost certainly, host-directed therapies will not be one-size-fits-all therapeutics. Although the sample size was small and the results can be considered preliminary, these types of studies of novel treatment strategies are sorely needed, especially in situations where safety and treatment effect are relatively unexplored. Wallis and colleagues provide valuable early efficacy and safety data to inform drug selection for larger trials and show that FEV_1, a known correlate of long-term mortality, is a feasible and potentially clinically meaningful endpoint for trials of host-directed therapies for tuberculosis.

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