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A RANDOMIZED CONTROLLED TRIAL OF HIGH-DOSE RIFAMPIN FOR PULMONARY TUBERCULOSIS

Clinical: (O) Tuberculosis and Other Opportunistic Infections

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Background: The standard of care for patients with pulmonary tuberculosis is a 6-month, 4-drug regimen that includes rifampin throughout. This blinded, randomized, controlled Phase II clinical trial (ClinicalTrials.gov NCT01408914) systematically examined the concept that increased rifampin doses could shorten standard therapy for tuberculosis and improve treatment outcomes without increased toxicity.
Methods: We randomized 180 adults with new, smear-positive, drug-susceptible pulmonary tuberculosis in equal numbers to receive 10, 15, or 20 mg/kg/day of rifampin during the 8-week intensive phase. The primary endpoints were: [1] change in elimination rate of *M. tuberculosis* log10 colony forming units (log10CFU) on 7H11 Middlebrook medium during the first 8 weeks of treatment (efficacy); and [2] frequency of grade 2 or higher rifampin-related adverse events occurring up to 4 weeks after intensive phase completion (safety). Safety was evaluated in the intention-to-treat (ITT, participants who received at least one dose of study medication) population. Efficacy was evaluated in the modified intention-to-treat (mITT, participants whose CFU data permitted sputum sterilization modeling) and per-protocol (PP, participants whose intensive phase rifampin dose was not altered by a protocol-defined study halt) populations.
Results: The ITT, mITT, and PP analyses included 180 (100%), 174 (96.7%), and 132 (73.3%) participants, respectively. Each 5 mg/kg/day increase in rifampin dose resulted in differences of -0.011 (95% confidence interval [CI], -0.025 – +0.002; P=0.230) and -0.022 (95% CI, -0.046 – -0.002; P=0.022) log10CFU/mL/day in the mITT and PP analyses, respectively. Faster count declines with rifampin AUC0-6 (P=0.011) were borderline significant with AUC0-6/MIC99.9 (P=0.053). The frequency of grade 2 or higher rifampin-related adverse events was similar across the three treatment arms: 26 (43.3%), 31 (51.7%), and 23 (38.3%) participants had at least one event (P=0.7092). The frequency of rifampin-related serious adverse events was also similar across arms: 1 (1.7%), 1 (1.7%), and 2 (3.3%) participants had at least one event (P=0.2679).
Conclusion: This is the first controlled study to show both dose- and exposure-response of rifampin on sputum culture sterilization. Rifampin doses of up to 20 mg/kg/day were safe compared to the standard dose of 10 mg/kg/day, with similar frequencies of rifampin-related adverse events.