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Abstract (oral session)

Pharmacokinetics, safety and effectiveness of high-dose rifampicin and moxifloxacin for tuberculosis meningitis: a randomised clinical trial in Indonesia

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Objectives: Tuberculosis meningitis (TBM) has a case fatality rate of >30%. Optimal treatment for TBM has not been established and follows the model of pulmonary TB treatment. Moxifloxacin, because of its potencyand good penetration into the cerebrospinal fluid (CSF) is a promising drug for TBM. Higher doses of moxifloxacin as well as rifampicin may increase drug exposure in blood and CSF, thereby improving survival. This study evaluates the pharmacokinetics (PK), safety and efficacy of such an intensified regimen for TBM in a hospital in Indonesia. Methods: We randomized 60 Indonesian TBM patients (10% HIV-infected) to standard dose (450 mg, 10 mg/kg) oral rifampicin or high dose (600 mg, 13 mg/kg) rifampicin administered i.v., and (in a second randomization) to moxifloxacin 400 mg, moxifloxacin 800 mg, or ethambutol 750 mg QD, for the first 14 days and in adjunction to standard INH, PZA and dexamethason. After the first two weeks of treatment all patients continued with standard TB treatment. Pharmacokinetic (PK) assessments were performed in blood and CSF within the first critical 4 days of treatment, adverse events attributable to TB treatment were assessed, and 1 month mortality was evaluated. This explorative study was powered to detect pharmacokinetic differences between groups. Results: So far PK data have been evaluated for 23 patients. Increasing the dose led to higher drug exposure in plasma for rifampicin (1.8 fold) and moxifloxacin (3-fold). Mean CSF concentrations for rifampicin were low and showed only a small increase with a higher dose (0.50 vs 0.37 mg/L). Mean CSF concentrations for moxifloxacin were 1.7 vs 3.9 mg/L ($p < 0.05$) for standard vs high dose moxifloxacin. Among the first 48 patients included, mild QTc prolongation occurred in 48% of patients taking moxifloxacin, while grade 3 (10%) and grade 4 (6%) hepatotoxicity was evenly distributed between groups. One-month mortality among the first 48 patients included, was substantially lower (31% vs 57%, $p = 0.07$) in patients taking high-dose rifampicin i.v. compared to those taking standard dose orally. Conclusion: Intensified antibiotic treatment for TBM leads to more favorable PK in plasma (rifampicin and moxifloxacin) and in CSF (moxifloxacin), with acceptable toxicity. Preliminary data in this explorative study show a trend for lower mortality in patients taking high dose rifampicin. Larger studies should evaluate the effect of intensified treatment on survival of patients with TBM.