O504
2-hour Oral Session
Frontiers in tuberculosis

Intensified antibiotic treatment for tuberculous meningitis; two phase 2 clinical trials conducted in Indonesia

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Background: Meningitis is the most severe form of tuberculosis (TB). Treatment is similar to pulmonary TB, even though cerebral penetration of drugs is suboptimal. Intensified antibiotic treatment may therefore improve outcome.

Material/methods: We conducted two clinical trials in Indonesia. First, we randomised 60 adult TB meningitis (TBM) patients to standard dose (450 mg oral, corresponding to 10 mg/kg) or high dose rifampicin (600 mg i.v) plus either oral moxifloxacin (400 mg or 800 mg) or oral ethambutol (750 mg) for the first fourteen days of TB treatment. Looking for an oral equivalent of high dose i.v. rifampicin we next randomised 30 adult TBM patients to either ~17mg/kg, ~20mg/kg of oral rifampicin, or ~13mg/kg of rifampicin given intravenously. Pharmacokinetic (PK) sampling was performed in blood and cerebrospinal fluid (CSF), tolerability and survival were monitored.

Results: From the first study (published; Ruslami et al, Lancet Infectious diseases 2013;13:27-35), a 33% higher dose of rifampicin given intravenously led to a three times higher rifampicin exposure in blood and CSF. Intensified treatment was well-tolerated and associated with significantly lower mortality (adjusted HR 0.42; 95% CI 0.2-0.91). Compared to patients who died during the two weeks of intensified treatment, patients who survived had significantly higher rifampicin exposure, both in blood and CSF. From exposure-response curves, a rifampicin plasma $AUC_{0\text{-}6h}$ of ~70 mg/L.h (~$AUC_{0\text{-}24h}$ of 116 mg/L.h) and C_{max} of ~22 mg/L were deduced as minimum target values for treatment.

In the second trial, a higher dose (~20mg/kg) of oral rifampicin resulted in roughly similar plasma $AUC_{0\text{-}24h}$ values as ~13 mg/kg rifampicin intravenously, but C_{max} plasma concentrations remained higher with intravenous administration. Cerebrospinal fluid (CSF) rifampicin was detectable in 22/26 patients, correlating with plasma $AUC_{0\text{-}24h}$ ($p < 0.001$) and C_{max} ($p = 0.019$). Liver transaminase increases were reversible upon continuation (grade 3; n=8) or stopping (grade 4; n=1) of treatment and were not related to exposure to rifampicin.

Conclusions: Treatment with high dose i.v. rifampicin during the first 2 weeks is safe, leads to higher drug concentrations in blood and CSF and better survival of TBM. Intravenous rifampicin is more difficult to administer and not widely available in TB-endemic settings, but an oral rifampicin dose with

equivalent drug exposure in blood and CSF was found. Further study is needed to examine if even higher doses rifampicin should be used to improve patient survival, and if the dosage of other drugs should be increased.