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Symposium

## [S-15] S-15: Applying TDM to HIV and TB therapy

Chairs: Dario Cattaneo, Italy / Lawrence Soon U Lee, Singapore

Wed. Sep 27, 2017 1:45 PM - 3:30 PM Main Hall (1F)

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### [S-15-4] Therapeutic drug monitoring of rifampicin & isoniazid and implications of acetylator genotype on plasma levels

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#### Background

Rifampicin(Rif) and Isoniazid(Inh), important first-line drugs in treatment of tuberculosis(TB), exhibits wide inter-individual variability. Factors like inadequate absorption, inaccurate dosing (as per mg/kg), altered metabolism, clinical conditions, drug-drug interactions or acetylator status of the individual etc. may interfere with drug exposure thus altering the bioavailability & causing a slow response to therapy. In the present study, we have assessed plasma rifampicin and isoniazid levels & correlated them with the acetylator status and other factors contributing to sub-optimal levels & response to therapy.

#### Methods

An in-house validated HPLC methods were used for plasma rifampicin and isoniazid level estimation. Therapeutic range for peak rifampicin and isoniazid levels is 8-24 mg/L and 3-6 mg/L respectively. Allelic variants from human NAT2 gene(\*6, \*11 and \*13) were genotyped by Tetra-ARMS PCR. A detailed clinical & drug history was obtained from 130 clinically proven Rif susceptible TB patients on ongoing Rif & Inh therapy.

#### Results

Among the study population, 75 patients(56%) had plasma Rif levels in the sub-therapeutic range while 2 patients(1%) had a toxic level. Isoniazid levels observed in 80 patients showed a sub-optimal & variable trend with 26 patients(33%) having sub-therapeutic levels & 20 patients(25%) had toxic levels. Among the NAT2 polymorphisms available for 50 patients so far, about 40%(n=20) were slow acetylators(carriers of NAT2\*6 allele) & 38%(n=19) were intermediate acetylators(carriers of \*11 & \*13 alleles) while remaining 22%(n=11) were rapid acetylators. Most of the slow acetylators had isoniazid levels at a higher side as compared to the intermediate and rapid acetylators. Plasma rifampicin levels were inversely proportional to the acetylator status. Thus most rapid acetylators had high rifampicin and low isoniazid levels. Other factors attributing to the variability in drug levels were food interaction (n=4), low body weight adjusted dose (n=31), extended treatment therapy i.e >6 months (n=15) etc.

#### Conclusions

The results of this study suggest that sub-optimal levels of rifampicin and isoniazid are common. A high prevalence of slow or intermediate acetylators suggest the importance of assessment of NAT2 gene

polymorphisms prior to dose initiation. Monitoring drug levels is necessary to optimize drug doses & achieve therapeutic efficacy & desired patient outcome.