Poster

[P25-3] P25-3: Anti-infective drugs (3): TB drugs

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[P25-3-6] Meta-analysis of NAT2 genotypes and the risk for anti-tuberculosis induced liver injury (AT-DILI)

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Background

NAT2 slow acetylators are known for delay in the metabolism of isoniazid causing anti-tuberculosis drug-induced liver injury (AT-DILI). The marked decrease in acetylation rate was observed among slow acetylators during the association study of bladder cancer and *NAT2* polymorphisms, which acetylator phenotypes are usually determined by caffeine test. This led to the proposed hypothesis of new subset within slow acetylators group, the “ultra-slow acetylator”. Ultra-slow acetylators are defined as individuals with *NAT2*6/*6, *6/*7, or *7/*7*. However, the influence of “ultra-slow acetylator” subset and the risk of AT-DILI are not clearly understood. Therefore, we performed genotype level meta-analysis to assess the risk of AT-DILI in all *NAT2* genotypes with special attention to ultra-slow acetylator genotypes.

Methods

Meta-analysis was based on the published studies that compared *NAT2* genotype frequencies between ATDILI and tolerant controls according to the quality control criteria. Systemic searches were conducted in PubMed, Scopus, ISI web of science, to identify the articles published up to 31 October 2016.

Results

The 822 cases and 4,630 controls were included from 18 studies. The slow acetylator genotypes can be assured by their robust association with ATDILI in meta-analysis over *NAT2*4/*4* except *NAT2*5/*5* (*5/*5: OR: 1.69; 95%CI: 0.96-2.95; *P*=6.79E-02, non-*5/*5 slow acetylator OR range from 2-5 with *p*- value 10^{-3}-10^{-10}). The association of NAT2 slow acetylator with AT-DILI was confirmed with OR: 2.80; 95%CI: 2.20-3.57; *P*=5.73E-18. Subgroup analyses of ultra-slow and all other slow acetylators demonstrated OR: 3.6; 95%CI: 2.30-5.63; *P*=1.78E-08 in ultra-slow acetylators; OR: 2.35; 95%CI: 1.69-3.27; *P*=3.65E-07 in all other slow acetylators. The comparison between ultra-slow versus all other slow acetylators cannot detect significant differences (*P*= 0.07).

Conclusions

The differences between ultra-slow and all other slow acetylators cannot be identified in our meta-analysis. However, variability in AT-DILI risk existed when compared each genotype against the *4/*4, and not all slow acetylator genotypes are contributing equally to the ATDILI genotype. *NAT2*6* and **7*-containing genotypes contributed to ATDILI more than *NAT2*5/*5* genotype. Personalized risk assessment based on *NAT2*

genotype status provides more precise risk estimation compared with conventional acetylator type classification for AT-DILI.