O424
1-hour Oral Session
Challenges in antifungal treatment

Intra-subject variability and exposure-response relationship of isavuconazole in the phase 3 SECURE study in patients with invasive mould disease caused by Aspergillus spp. and other filamentous fungi

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Background: Isavuconazonium sulfate is the water-soluble prodrug for oral and intravenous administration of the active moiety isavuconazole (ISAV), a broad-spectrum triazole antifungal recently authorized in the EU and US. The ISAV intravenous formulation contains no cyclodextrin, and the oral formulation is highly bioavailable with no food effect. ISAV shows dose-proportional pharmacokinetics. Moderate inter- and intra-subject variability of ISAV plasma levels was shown in healthy subjects, and demonstration of similar results in patients with invasive mould disease (IMD) may support a simplified therapeutic drug monitoring (TDM) approach compared to existing treatments. This *post hoc* analysis of the SECURE trial assesses the intra-subject variability in ISAV trough levels.

Material/methods: SECURE was a large (N=516), Phase 3, double-blind, randomised trial comparing ISAV with voriconazole in primary treatment of IMD caused by *Aspergillus* spp. and other filamentous fungi. ISAV was administered 200mg IV TID for 2 days, then 200mg QD (IV or oral). ISAV blood samples were taken on Days 7, 14, 42, at end-of-treatment (EOT), and 4 weeks after EOT. Repeated protocol-defined ISAV trough levels (1 hour prior to next morning dose or 24±1 hours after last dose) were available from 76 patients with proven, probable, or possible IMD. The first available individual trough level for each patient was compared to any available subsequent trough level to determine the maximum change (decrease or increase). Intra-subject variability was assessed by coefficient of variation (CV). The association between first trough levels and success rates at EOT, as assessed by a blinded Data-Review Committee, was also analysed.

Results: All patients had detectable ISAV plasma levels at all on-treatment time points. Trough levels increased from the first to subsequent blood samples in 46 patients (61%) and decreased in 30 patients (39%). The respective mean first trough levels were 3.21 and 3.55 µg/mL (total mean and standard deviation: 3.34±1.44 µg/mL). Median increase was 43% (range 0.5–206%), median decrease was 29% (4–84%). In 39/46 patients (85%), increases were < 100%; in 24/30 patients (80%), decreases were < 50%. The median intra-subject CV was 22% (90%CI: 19–25%), mean 26% (90%CI: 22–30%). Analysis of success rates at EOT by quartiles of initial ISAV trough levels showed clinical success rates of 89%, 84%, 89% and 79%, and overall success rates of 47%, 53%, 58% and 63% (mean ISAV levels across quartiles: 1.80, 2.70, 3.58 and 5.28 µg/mL).

Conclusions: Intra-subject variability on trough levels in patients with IMD treated with ISAV was < 30%, supporting predictable pharmacokinetics of ISAV in the clinical setting, and suggesting that a sparse sampling schedule may be sufficient in patients followed with TDM. No clear correlation was observed in the analysis of success rates by quartiles of trough levels.