EP018

ePoster Session

Fungal infections: diagnosis and management

A comparison of the safety profiles of isavuconazole vs voriconazole in the phase 3 SECURE study in patients with invasive mould infections

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Objectives: Isavuconazole (ISA) is the active moiety of isavuconazonium sulfate, a water-soluble prodrug for oral and intravenous administration. ISA has broad-spectrum antifungal activity against invasive mould disease (IMD). SECURE was a large (N=516), Phase 3, double-blind, randomized trial which demonstrated non-inferiority of ISA compared with voriconazole (VRC) for Day 42 all-cause mortality (ISA 18.6%, VRC 20.2%) in primary treatment of IMD caused by *Aspergillus* spp. and other filamentous fungi. Assessment of safety was a study objective, and is particularly important in these severely-ill IMD patients with multiple co-morbidities.

Methods: A treatment-emergent adverse event (TEAE) was any AE after first study drug administration until 28 days after last study drug administration. TEAEs were collected at every visit. The numbers (%) of patients with TEAEs were summarized by System Organ Class (SOC) and preferred term (PT) (MedDRA v12.1), and were compared by SOC (ISA vs VRC) using Fisher's exact test. Alanine-aminotransferase/aspartate-aminotransferase (ALT/AST) levels were summarized on Days 7, 14, 28, 42, at end-of-treatment and 4 weeks thereafter, categorized by exceeding threshold multiples of the upper limit of normal (ULN).

Results: 97% of patients reported TEAEs regardless of causality (ISA 96% [247/257], VRC 98% [255/259]), which was expected considering the severely-ill study population.

When analyzed by SOC, TEAE rates were lower with ISA vs VRC in 19 of the 24 SOCs with reported TEAEs. TEAE rates were ≥ 5% lower with ISA vs VRC in disorders of eye (15% vs 27%, $p<0.05$), skin (33% vs 42%, $p<0.01$), hepatobiliary (9% vs 16%, $p<0.05$), psychiatric (27% vs 33 %, ns) and cardiac (17% vs 22%, ns). Moderate or severe TEAEs were lower with ISA vs VRC in 21 of the 24 SOCs.

The rate of treatment-related TEAEs was overall significantly lower with ISA (42%) vs VRC (60%) ($p<0.01$).

This difference in favor of ISA vs VRC was primarily influenced by disorders of eye (3% vs 11%, $p<0.01$), hepatobiliary (2% vs 10%, $p<0.01$), investigations (including hepatic enzyme elevations) (10% vs 18%, $p<0.01$) and psychiatric (2% vs 11%, $p<0.01$). TEAEs of respiratory disorders were lower with VRC (2%) vs ISA (6%, $p<0.05$).

The lower rate of treatment-related hepatobiliary events with ISA vs VRC was primarily influenced by PTs of hepatic function abnormal, hyperbilirubinemia, cholestasis, hepatic failure and jaundice. This was further supported by a lower rate of ALT/AST (> 3 x ULN) plus bilirubin (> 2 x ULN) elevations at the end-of-study visit (ISA 0.4% vs VRC 2.7%).

Conclusion: In the SECURE study, ISA was better tolerated than VRC. This difference was most evident for hepatic (both clinical events and transaminase elevations), skin, eye and psychiatric adverse effects. The consistency of the differences in favor of ISA in moderate or severe TEAEs underlines the potential clinical relevance of the safety results.