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Dosage individualization of voriconazole for immunocompromised patients

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Background: Voriconazole (VCZ) is a first-line agent for the treatment and prevention of invasive fungal infections (IFIs). It has a narrow therapeutic range. In adults, the extreme VCZ pharmacokinetic (PK) variability and non-linear PK behaviour means that dosage adjustment may result in disproportionate changes in drug exposure with the associated risk of therapeutic failure or toxicity. There are no algorithms that enable dosage to be reliably adjusted to achieve desired concentrations in a timely and precise manner. Given the persistent high morbidity and mortality of IFIs, novel ways to deliver optimized VCZ therapy are urgently required.

Material/methods: A single-center Phase II trial was conducted. Patients were recruited from the Haematology/Bone Marrow Transplant wards at the Royal Liverpool Hospital. All patients received VCZ for prophylaxis as a standard-of-care. Patients were provided written informed consent. The primary endpoint was the proportion of patients having a trough concentration 1-3 mg/L at the end of DI10. The standard loading dose of VCZ at 6 mg/kg q12h was given at dose interval (DI) 1 and 2. A single standard maintenance dose of 4 mg/kg was also given at the start of the DI3. Plasma samples were taken within the second DI at 0,2,3 and 6 h post-infusion. At DI 4, patients received an individualized dose calculated using BestDose® software and the patient´s individual plasma concentrations. Further plasma samples were taken during DI4 and DI6. Patients had a further dose adjustment for DI 6 onwards. Five plasma samples were taken again at the end of DI 10 to determine if patients had achieved the desired target 1-3 mg/L. After 5 days of therapy (10 DI), all antifungal

therapy and the duration of VCZ therapy was at the treating physician´s discretion. All VCZ concentrations were measured with LC/MS/MS under.

Results: Five patients were recruited. Age (mean ± SD)/range was: 56.4±8.4/45-67 years old. Weight was: 83.54 ± 10.5/73.4-96 kg. Three patients (60%) were male. Two patients had a myelodysplastic syndrome undergoing allogeneic stem cell transplant (SCT); one patient a follicular lymphoma; one patient a mantle cell lymphoma and another patient an acute myeloid leukaemia, also undergoing SCT. They all received VCZ for therapy/prophylaxis. All patients (100%) achieved the desired target 1-3 mg/L at the end of DI 10. An example is shown in figure. No serious adverse events were reported.

Conclusions: This is the first study prospectively evaluating the efficacy and safety of computer software in order to truly optimize and individualize antifungal therapy in patients with/at risk of IFIs. In this study, BestDose® was able to predict the VCZ dose needed to achieve the optimal target concentrations after 5 days of therapy.