Pd-targets for voriconazole and posaconazole

Based on the estimates of the PD-targets for voriconazole and posaconazole we can now determine if there remains a role for voriconazole or posaconazole in the management of azole-resistant disease. The integration of all above information is given in Table 5 for voriconazole and Table 6 for posaconazole. The underlying resistance mechanisms are provided for each MIC-value. Based on the estimates of the PD-target, the exposure can be calculated that is needed to achieve the PD-target for each MIC. The exposure corresponds with plasma levels, which are typically higher than those needed for treating infection due to wild-type isolates. The feasibility of achieving higher exposure depends on characteristics of the drug related to absorption and clearance, but is limited by toxicity.

For voriconazole, a total drug AUC/MIC ratio of 21. 96 was associated with 50% probability of success (EI50) to suppress galactomannan concentrations in a dynamic in vitro model of the human alveolus (Jeans et al., 2012). Using an immunocompetent murine model of invasive aspergillosis, we observed that achieving a serum total AUC0–24 /MIC ratio of 17. 61 was the PD-target linked to halfmaximum antifungal effect predicting therapeutic success (Table 4) (Mavridou et al., 2010b). Although, the calculated pharmacodynamic index (using total drug) is similar for both studies, one should consider that in vitro simulation of in vivo protein binding by adding serum proteins in the in vitro models is difficult since complex phenomena may take place (Smith et al., 2010). Given the qualitative and quantitative differences between human and bovine serum, the unbound fraction of various drugs was markedly different between human and bovine serum (Finlay and Baguley, 2000). Such differences were found for

voriconazole in the serum of human and different animals (Roffey et al., 2003). It is generally accepted that only the unbound fraction of drug is pharmacologically active and therefore when in vitro concentrations are correlated with in vivo concentrations, in vivo drug exposures should be corrected for the protein binding (Zeitlinger et al., 2011). This can alter the PD of voriconazole depending on the protein-binding differences between 2% fetal bovine serum and 100% human serum.

Recently, Pascual et al. performed a population pharmacokinetic analysis (NONMEM) on 505 plasma concentration measurements involving 55 patients with invasive mycoses who received recommended voriconazole doses in order to describe factors influencing the pharmacokinetic variability, to assess associations between plasma concentrations and efficacy or neurotoxicity/hepatotoxicity, and to define intravenous and oral doses required for achieving drug exposure with the most appropriate efficacy/toxicity profile (Pascual et al., 2012). A logistic multivariate regression analysis revealed the therapeutic target with a clinically appropriate efficacy-safety profile, close to that recently reported by others (Seyedmousavi et al., 2013e). An independent association between voriconazole trough concentrations and probability of response or neurotoxicity was identified for a therapeutic range of 1. 5 mg/L (> 85% probability of response) to 4. 5 mg/L (<15% probability of neurotoxicity). Population-based simulations with the recommended 200 mg oral or 300 mg intravenous twice-daily regimens predicted probabilities of 49% and 87%, respectively, for achievement of 1. 5 mg/L and of 8% and 37%, respectively, for achievement of 4. 5 mg/L. With 300–400 mg twice-daily oral doses and

200–300 mg twice-daily intravenous doses, the predicted probabilities of achieving the lower target concentration were 68–78% for the oral regimen and 70–87% for the intravenous regimen, and the predicted probabilities of achieving the upper target concentration were 19–29% for the oral regimen and 18–37% for the intravenous regimen (Pascual et al., 2012). Apparently, patients achieving higher concentrations of voriconazole may show higher exposure and a better response to therapy, but they are at higher risk for toxicity. In contrast, patients achieving lower concentrations may have reduced therapeutic response but subsequently a lower risk for adverse events.

Whereas the Pascual study is based on trough levels as a measure of exposure (Pascual et al., 2012), because it is much easier to determine than the AUC, all preclinical models are AUC based (Jeans et al., 2012; Mavridou et al., 2010b; Seyedmousavi et al., 2013a). However, voriconazole trough levels correlate well with AUC as determined in several studies. Estimates of total AUC0–24 in sixty-four healthy subjects showed that standard dose on the basis of 200 mg twice daily oral voriconazole results in a total AUC value of 18–23 mg. h/L (Purkins et al., 2003). Population PK modeling of voriconazole in 21 healthy volunteers, and 43 patients with proven or probable invasive aspergillosis, (Hope, 2012) and other PK studies in allogeneic haematopoietic stem cell transplant recipients (Fig. 1) (Bruggemann et al., 2010a), revealed that the trough concentration are well correlated with the AUC, and a drug level of 1 and 4. 5 mg/L corresponded with a total AUC0–24 of 43 and 151 mg h/L, respectively.

The AUC levels required for efficacy as derived from the trough levels in the Pascual study (Pascual et al., 2012), correspond well with the AUC levels required for efficacy in preclinical models. The threshold was consistent with minimum inhibitory concentration required to inhibit the growth of 90% of organisms and epidemiological cutoffs of most VRC-susceptible fungal species, as well as clinical reports (Espinel-Ingroff et al., 2010; Pfaller et al., 2011; Verweij et al., 2009a) (Arendrup et al., 2012a; Hope et al., 2013; Rodriguez-Tudela et al., 2008).

Assuming no resistant strains in the Pascual study (Pascual et al., 2012), the ECOFF of voriconazole (1 mg/L) can be used as the upper value of the MIC distribution and the denominator in the AUC/MIC. In addition, using EUCAST methodology, Jeans et al. reported that the trough concentration/MIC values that achieve optimal efficacy was 1 (Jeans et al., 2012). However, considering both wild-type and mutant population of A. fumigatus, higher ECOFF is required for voriconazole (2 mg/L) (van Ingen et al., 2014). Given this, the upper value of denominator will be 2 mg/L and the AUC/MIC ratio required for optimal treatment is 43. It follows that the AUC/MIC ratio required for optimal treatment is very close to the pharmacodynamic targets derived from preclinical models (EI50 EUCAST: 17. 61–21. 96) in order to achieve therapeutic success considering the differences in voriconazole disposition between human and mouse.

Therefore, it can be expected that isolates with a MIC that is classified as susceptible can be treated with voriconazole, with a probability of exposure attainment of over 90% according to population pharmacokinetics modeling of Hope et al. using licensed doses of voriconazole (Hope, 2012; Hope et al.,

2013). For isolates with a voriconazole MIC of 2 mg/L, classified as intermediate susceptibility by Verweij et al. (2009a), the plasma level should exceed 1. 03 mg/L which is well attainable. Voriconazole MIC of 4 mg/L is classified as resistant, and in order to achieve the PD-target a higher exposure is needed (≥2. 65 mg/L). Higher exposure of voriconazole can be achieved using dose escalation, but will be associated with increased probability of toxicity. Clearly if voriconazole would be used in this setting intravenous administration would be required as well as close monitoring of plasma levels. For isolates with a MIC exceeding 4 mg/L very high plasma levels exceeding 5. 30 mg/L are needed, which are in a range where toxicity can be anticipated.

Posaconazole is currently not licensed for the primary therapy of invasive aspergillosis, but may be used for salvage therapy. Similar to the other triazoles, posaconazole displays concentrationdependent with time dependence pharmacodynamic characteristics, for which a total AUC0–24 /MIC ratio ranging 167–178 was the value predictive of success associated with half-maximal efficacy. Estimates of the total AUC0–24 for patients infected with A. fumigatus with a posaconazole MIC of 0. 125 mg/L receiving 800 mg/day are 13–17 mg. h/L, corresponding to the best response rate (AbuTarif et al., 2010; Ullmann et al., 2006). Our calculation (Table 6) also showed that similar exposure (AUC0–24 10. 43–11. 12 and AUC0–24 20. 87–22. 5) are required to achieve optimal response for the isolates with MIC 0. 64 and 0. 125 mg/L, respectively. On the other hand, optimal outcome could be achieved with posacona- zole plasma concentrations of ~0. 7 mg/L when administered for prophylaxis. However, for purpose of salvage therapy,

Walsh et al. showed that an average concentration of 1. 25 mg/L was associated with a higher probability of a clinical response for patients with invasive aspergillosis receiving posaconazole 800 mg/day (Walsh et al., 2007), corresponding to an AUC of approximately 30 mg h/L. Therefore, with fixed dosing of 800 mg/day (200 mg four times a day), drug exposures may not be high enough to cover the entire wild-type distribution, reliably in persistently neutropenic hosts with invasive aspergillosis. The patients infected with an Aspergillus strain with a MIC of 0. 25 mg/L, will need to obtain an AUC0–24 of ~40–50 mg. h/L, which corresponds with trough concentrations of > 1. 25 mg/L, as shown in Fig. 1 (Bruggemann et al., 2010a, b).

According to available data shown in Table 6, the exposure needed to treat infection due to isolates that are classified as susceptible can only be achieved with a low probability of exposure attainment in isolates with the MIC ranging 0. 31–0. 125 mg/L (Arendrup et al., 2012a; Verweij et al., 2009a). Given the current problems of increasing the exposure of the drug due to its formulation and limited absorption, there appears to be no room for posaconazole for the treatment of isolates that are not within the wild type distribution. However, a new oral tablet and intravenous formulation are under development and soon to be brought the clinical practice (Krishna et al., 2012b). The tablet is designed to release the entire dose of solubilized posaconazole in the small intestine, maximizing systemic absorption. In an exploratory study, this new solid oral formulation significantly increased exposure to posaconazole relative to the oral suspension in fasting healthy volunteers (Courtney et al., 2004; Krishna et al., 2009, 2012a). Following

single and multiple doses of posaconazole solid oral tablets (200 and 400 mg) in healthy subjects, the exposure increased in a dose-related manner. When the dose was increased in a 1: 2 ratio, exposure increased in 1: 1. 9 and 1: 1. 8 ratios for days 1 and 14, respectively. On day 1, the dose-normalized posaconazole exposure (AUCtau) was substantially higher than for the oral suspension under both fasted and fed conditions (Krishna et al., 2012a). Notably, a novel cyclodextrin formulation of posaconazole is under development for intravenous (i. v) use. In a phase 1B study, the pharmacokinetics of two doses of i. v. posaconazole was investigated in 55 patient volunteers (Maertens et al., 2012). The higher protective blood level of posaconazole was found for the 300 mg given once daily, for which the average blood concentration at 14 days was 1. 43 mg/L. The minimum effective concentration was seen in 95% of patients. Recently, Cornely et al. reported that 300 mg posaconazole i. v. was well tolerated and resulted in higher exposure compared to the oral suspension (Cornely et al., 2013). A lowest mean Cmin value of 1297 mg/L was achieved for posaconazole i. v 300 mg vs. 751 mg/L for posaconazole oral suspension. Although our calculations indicate that a posaconazole exposure of ≥3. 33 mg/L wouldbe required to treat infection due to isolates with a posaconazole MIC of 0. 5 mg/L, we believe that this might be achievable using the i. v. formulation. Given that a significant proportion of isolates harboring an azole resistance mechanism exhibit a posaconazole MIC of 0. 5 mg/L, this approach requires further investigation in experimental models.