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Isavuconazole prophylaxis among solid organ transplant recipients: effectiveness and drug interaction with tacrolimus

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Background: The role of isavuconazole (ISA) as prophylaxis in solid organ transplant (SOT) is not known. We initiated universal ISA prophylaxis (lungs, 4 months (m); others 1 mo) following a cluster of zygomycosis cases among patients receiving voriconazole prophylaxis.

Material/methods: This is a prospective, observational study of consecutive patients undergoing SOT at a single hospital from 10/1/15 through 7/31/2016 who received ISA prophylaxis. Our goals were to evaluate the efficacy of ISA prophylaxis and describe its interaction with tacrolimus (TAC).

Results: 187 patients were enrolled: 60 lung, 51 kidney, 53 liver, 16 heart, small bowel (4) and pancreas (3). ISA was prematurely stopped due to side effects in 5%; in all except one instance, premature discontinuation occurred in lung transplant recpients. GI intolerance predominated. 3% developed breakthrough infections: 3 due to *Candida* (1 candidemia; 2 intra-abdominal infections), and 2 due to *Aspergillus fumigatus* (1 was colonized before transplant; 1 with unsuspected pulmonary aspergillus found in the explanted lungs). For TAC interaction with ISA, we focused on 59 patients who had ≥5 and ≥3 TAC levels performed while on (total levels n=641) and off (n=459) ISA prophylaxis, respectively. TAC concentration/dose (C/D) were highest on day 4, then decreased and stabilized ~ day 8, reflecting the effect of ISA loading doses. While on ISA, TAC C/D was higher among liver recipients (median, 192) than kidney (124), lung (106) and heart (105, p=0.002). There was considerable inter-patient variability of TAC C/D. After ISA was discontinued, TAC C/D gradually decreased and stabilized at ~week 4. The median TAC C/D on ISA was higher than C/D off ISA (122 and 104 (ng/mL)/(mg/kg), respectively); p=0.003). Indeed, for all transplant recipients, the C/D on ISA was reduced by 22.4% after ISA was discontinued. Liver transplant recipients experienced the largest TAC C/D reduction (55%) compared with other organ recipients (22% heart, 17% lung and 15%

kidney; p=0.045). The difference in TAC C/D between SOT groups was no longer present. While on ISA, race (p=0.07), BMI (p=0.00001), and liver transplant (p=0.00001) were associated with TAC C/D ratios. By multivariate analysis, BMI and liver transplant recipients were factors independently associated with C/D ratios. Off ISA, BMI was the only factor associated with C/D.

Conclusions: ISA is effective as antifungal prophylaxis after SOT, associated with low rates of candidiasis and aspergillosis, and no further Zygomycosis ISA exerts significant drug interaction with TAC in SOT recipients, resulting in decreased TAC concentration after ISA is discontinued. Given considerable inter-patient variability in the magnitude of drug interaction, TAC dose reductions should be individualized. Factors associated with TAC C/D were BMI and liver transplant. ISA exerts interaction on TAC for a median of 4 weeks, reflecting its long half-life and large volume of distribution.