Risk Factors for Failure of Primary (Val)ganciclovir Prophylaxis Against Cytomegalovirus (CMV) Infection and Disease in Solid Organ Transplant (SOT) Recipients

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BACKGROUND
• Following solid organ transplantation (SOT), the optimal dose of primary (val)ganciclovir prophylaxis against CMV infection is debated1
• Viral breakthrough infection and treatment-limiting side effects are frequently seen1-3

AIMS
• To investigate to what extent different dosages of (val)ganciclovir prophylaxis affect the risk of experiencing prophylactic viral breakthrough during active administration of prophylaxis
• To identify reasons and risk factors for premature prophylaxis discontinuation

METHODS
• All SOT recipients ≥18 years of age transplanted (tx) between 2012-2016 at Rigshospitalet, and who were initiated on primary prophylaxis ≥14 days post-tx were followed from this time (baseline) until 90 (±7) days post-tx
• A prophylaxis score for each patient/day was calculated during the follow-up time (score of 100 corresponding to the manufacturers’ recommended dose for a given eGFR) (Figure 1)
• Score = actual dose (mg) / optimal dose (mg) adjusted for eGFR x 100
• Prophylaxis breakthrough was defined as PCR verified CMV DNA positivity in plasma or BAL (i.e. infection) and premature stop of prophylaxis as >7 days with a score of 0
• Time to event and hazard ratios (HR) were estimated with Cox models after adjustment for relevant risk factors

RESULTS
• Of 585 SOTs (311 kidney, 117 liver, 106 lung, 51 heart) included, 41 (7%, 95% CI 4.9-9.1%) experienced CMV prophylaxis breakthrough (Figure 2 and Table 1), of which 9/41 (22%, 9.2-34.6%) developed viral resistance to (val)ganciclovir
• 33/585 (5.6%, 3.7-7.5%) ceased prophylaxis for other reasons during the first 90 days after tx (Figure 3)
• After adjustment for tx type, CMV IgG D+/R- mismatch and increasing % of FUT with a prophylaxis score < 90 were associated with increased risk of breakthrough (HR 4.83 [95% CI 2.39-9.79] p<0.001 and HR 1.14 [1.03 - 1.28] p=0.016/10% longer follow-up time with a score < 90 respectively) (Figure 4) whereas tx type was not
• Main risk factor for stopping prophylaxis for reasons other than breakthrough was lung tx (HR 13.11 (versus kidney SOT) [2.47-69.70] p=0.003), mainly due to liver or myelotoxicity (Table 2)

CONCLUSIONS
• SOTs receiving (v)gcv primary prophylaxis doses below the manufacturers’ recommended doses according to latest eGFR were at an increased risk of CMV prophylaxis breakthrough, particularly in case of CMV IgG D+/R- mismatch
• Lung tx recipients are at a higher risk of premature prophylaxis discontinuation
• Adjusting the administered dosage of prophylaxis according to the current eGFR is important, as well as acknowledging the continued need for newer and less toxic agents against CMV

TABLE 1. Baseline Characteristics of 585 SOT Patients, Stratified For Breakthrough Infections and Prophylaxis Discontinuation

REFERENCE