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A phase II randomized double-blind placebo-controlled trial of ganciclovir to prevent cytomegalovirus (CMV) reactivation in acute critical illness ["GRAIL"]

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Background: CMV reactivation occurs frequently in non-immunosuppressed adults with critical illness and is associated with worse outcomes. Whether CMV is a marker or cause of adverse outcomes is unknown. The objectives of this study were to assess the feasibility, safety, and explore clinical outcomes of ganciclovir prophylaxis to prevent CMV reactivation non-immunosuppressed adults with critical illness.

Material/methods: We conducted a multicenter, randomized (stratified by site and trauma vs sepsis), double-blind, placebo-controlled trial [NCT01335932] of prophylaxis with ganciclovir (5mg/kg IV twice daily for 5 days, then either IV ganciclovir or oral valganciclovir once daily until hospital discharge) in mechanically-ventilated adult CMV seropositive adults with sepsis or trauma. The primary endpoint was the change in serum IL-6 between days 1 and 14 between groups. Clinical and laboratory outcomes were analyzed with parametric and non-parametric methods.

Results: The intent to treat (ITT) population included 72 placebo and 84 ganciclovir patients. Key cohort characteristics were 57% male, 88% sepsis, median Apache III score 71, and were similar between groups. The incidence of neutropenia (absolute neutrophil count <500 cells/L), red blood cell or platelet transfusions, or renal dysfunction (glomerular filtration rate <60 mL/minute) was not statistically different between groups ($p>0.05$, all comparisons). The key clinical outcomes between groups (ITT population) are shown in Table 1. In pre-specified analyses of the sepsis subset by day 28, the median number of mechanical ventilation days trended lower in the ganciclovir group: 6 vs 5 days, $p=0.06$, and the number of VFDs was significantly higher in the ganciclovir group: 23 vs 20 days, $p = 0.03$. There were no significant differences between groups for other clinical endpoints ($p>0.05$ for all comparisons).

Conclusions: Ganciclovir was safe, effectively prevented CMV reactivation, and was associated with a reduction in duration of mechanical ventilation and an increase in ventilator-free days among patients with sepsis. An efficacy trial of CMV prophylaxis in CMV seropositive adults with sepsis is warranted.

Key clinical outcomes by day 28 (ITT population)	**Placebo (n=72)**	**Treatment (n=84)**	**P-value**
Difference in serum IL-6 between days 1 and 14, mean log10 units	-0.79	-0.79	1.0
Cumulative incidence of plasma CMV reactivation (any level)	28 (39%)	10 (12%)	<0.0001
Days of mechanical ventilation, median [IQR]	6 [3-12]	5 [3-9]	0.16
Ventilator-free days, median [IQR]	19.5 [8-24]	23 [16-25]	0.049
Secondary bacteremia or fungemia (number, %)	11 (15%)	15 (18%)	0.83
ICU LOS, median [IQR]	8.5 [5-15]	8.5 [4-14]	0.76
Hospital LOS, median [IQR]	13 [8-23]	14 [8-22]	0.92
Mortality	11 (15%)	10 (12%)	0.54