#236

Valganciclovir Effects on Gut and Pulmonary Epithelial Barrier Markers in Treated HIV

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Background

- Asymptomatic CMV co-infection is hypothesized to contribute to immune activation, morbidity and mortality during treated HIV.
- The CMV drug, Valganciclovir, broadly suppressed markers of innate and adaptive immune activation in a trial of people with HIV (PWH) with incomplete CD4 recovery during antiretroviral therapy (ART).
- As CMV replicates in and is shed from gut and pulmonary mucosa, we hypothesized that valganciclovir might affect soluble markers of gut and pulmonary epithelial barrier function.

Methods

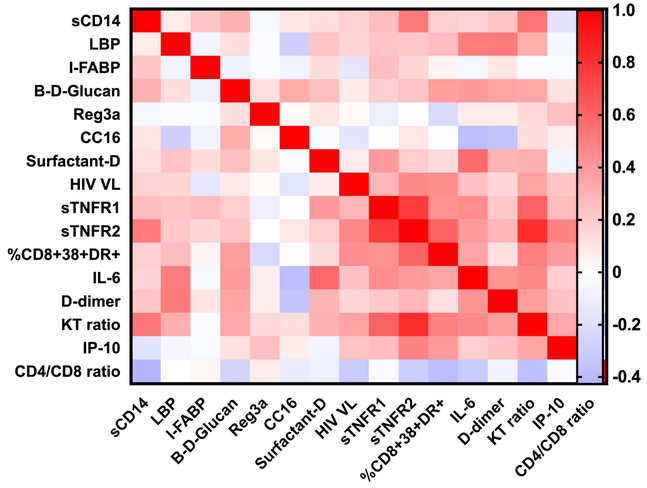
- **Design:** Cryopreserved plasma was assessed from a randomized placebo-controlled trial of valganciclovir (900mg daily for 8 weeks) among 30 HIV/CMV co-infected individuals with incomplete ART-mediated CD4 recovery and high CD8+ T cell activation (>10% CD38+HLA-DR+ CD8+ T cells).
- **Biomarkers** were assessed by commercial ELISA in duplicate every 4 weeks including:
- Markers of gut barrier dysfunction: sCD14, LPS binding protein [LBP], intestinal fatty acid binding protein [I-FABP], B-D-glucan, and regenerating islet-derived protein-3a [Reg3a] – a protein luminally secreted by intestinal epithelial cells).
- Pulmonary barrier dysfunction: (clara cell secretory protein [CC16] and surfactant D).
- **Analysis**:
  - Changes from baseline at each timepoint were compared between arms with linear mixed models, log-transforming variables and normalizing to the baseline interquartile range (IQR) to facilitate comparisons between biomarkers.
  - Correlations between biomarkers (including previously reported analytes) at baseline assessed with Spearman's rank correlation coefficients.

Results

Characteristics of ART-treated CMV+ Participants

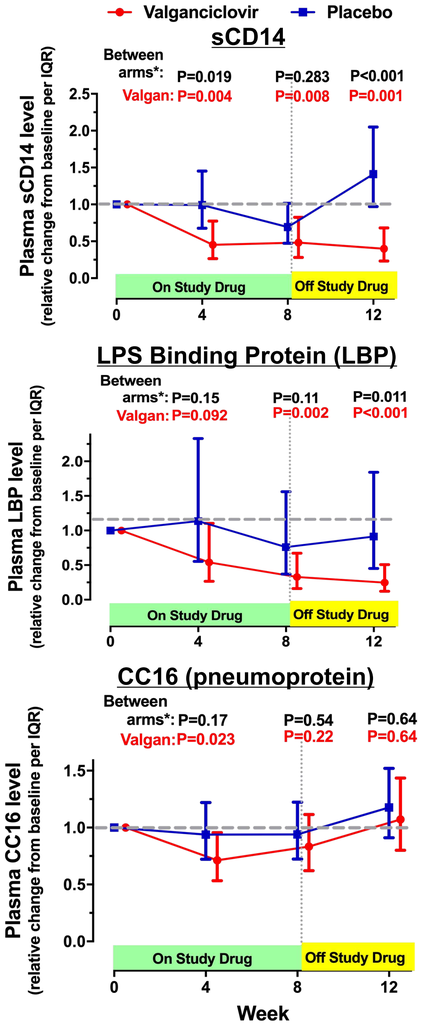
Characteristic	Valganciclovir Median (IQR) N=14	Placebo Median (IQR) N=16
Age, years	48 (43-55)	50 (44-59)
Male gender, N (%)	12 (86)	16 (100)
Plasma HIV RNA <75 c/ml, N (%)	10 (71)	11 (69)
Months on ART	28 (16-40)	27 (17-35)
CD4+ T cell count, cells/mm^3	207 (186-249)	187 (108-218)

Correlations Between Biomarkers at Baseline



- *There were significant correlations between sCD14 and both I-FABP and B-D-glucan (rho: 0.19-0.21, P<=0.05), but not with other putative measures of gut barrier integrity.*
- *There was no evidence for a relationship between the pneumoprotein CC16 and other plasma markers, but Surfactant D appeared to be associated with sTNFR1 (rho: 0.39, P=0.03) and IL-6 (rho: 0.58, P=0.002).*

Vaganciclovir Reduces Some Gut & Pulmonary Markers



Little Evidence for Changes in Other Biomarkers

Plasma Biomarker	Relative Change from Baseline Per Interquartile Range in Baseline Level (95% CI)					
	Valganciclovir			Placebo		
	Week 4	Week 8	Week 12 (off drug)	Week 4	Week 8	Week 12 (off drug)
Gut Markers						
I-FABP	0.6 (0.3-1.4)	1.4 (0.6-3.3)	0.9 (0.4-2.0)	0.7 (0.3-1.8)	1.2 (0.5-2.9)	1.1 (0.4-2.0)
B-D-Glucan	0.4 (0.1-1.7)	0.6 (0.1-2.4)	0.2 (0.1-1.0)	0.6 (0.1-2.7)	0.6 (0.1-2.9)	0.2 (0.03-0.8)
Reg3a	0.9 (0.6-1.3)	0.8 (0.6-1.2)	0.9 (0.6-1.3)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	0.9 (0.7-1.1)
Pulmonary Marker						
Surfactant D	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.4)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.8-1.3)

Conclusions / Interpretations

- Valganciclovir significantly reduces sCD14 and LPS binding protein in ART-suppressed PWH with incomplete CD4+ T cell recovery.
  - *As other more specific markers of gut barrier integrity were not affected, it is unclear if these changes reflect improved gut barrier defects or a non-specific effect on systemic immune activation.*
- Valganciclovir also tended to decrease the pneumoprotein CC16 in the valganciclovir arm, but the effect was transient and not significantly different than placebo.
  - *If real, it is unclear whether this change reflects a true improvement in pulmonary barrier function or simply decreased TNF signaling.*

Limitations / Future Directions

- Unclear whether these valganciclovir effects on biomarkers are mediated primarily by suppressing CMV vs. other herpesviruses.
- Unclear whether treating asymptomatic CMV co-infection might also reduce immune activation in individuals with higher CD4 counts.
- Given high within-subject variability for some of these analytes and the potential for greater effects with longer treatment duration, a longer and larger trial of treating asymptomatic CMV infection is required to definitively test these hypotheses *in vivo*.
- Valganciclovir has too many toxicities to consider its long-term use to reduce morbidity and mortality in treated HIV infection.
- Letermovir is a novel CMV terminase inhibitor that has been FDA approved for CMV prophylaxis in allogeneic hematopoietic stem cell recipients.
- The upcoming Letermovir trial in the ACTG (A5383) among ART-suppressed PWH presents an opportunity to address whether longer-term treatment with a specific CMV inhibitor can reduce markers of gut and pulmonary barrier dysfunction.

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