CVLs from Women Vaginally Administered PC-1005 Inhibit HIV-1 and HSV-2 in the Mucosa

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BACKGROUND

- The Population Council’s microbicide gel (PC-1005) containing 50µM MV-150 (M), 14mM Zinc acetate dihydrate and carrageenan (CG) protect macaques against single high dose SHIV-RT challenge vaginally for up to 8h (1, 2), significantly reduces HSV-2 shedding in macaques (3) and HSV-2 and HIV infections in murine models (2).
- A recent Phase 1 trial demonstrated that PC-1005 gel applied vaginally once daily for up to 14 days is safe and well tolerated (4, 5).
- Cervico-vaginal lavage samples (CVLs) collected 4h or 24h after last gel application showed MV-150 and CG dose-dependent inhibition of HIV-1 and HSV, respectively, in cell-based assays (4, 5).
- This pharmacodynamics study aimed to test activity of CVLs collected 4h or 24h after last gel application against HIV only and HIV-1/HSV-2 infection in human cervical mucosa.

RESULTS

- CVLs were collected as in Fig. 1. (a) non-antimicrobial explants were challenged with 500 TCID50 of HIV-1BaL (three explants per condition) 18h in the presence of 1/2 diluted CVLs then washed and cultured for 14d. Alternatively, tissues were pre- incubated with CVLs for (f) 15h or (g) 4h before viral challenge and cultured as described in (A). Infection was monitored by real time HIV gag qRT-PCR using culture supernatants (individual replicate analysis). Shown are summary results (Mean values of n = 3-15 experiments).
- CVLs do not decrease tissue viability.
- Baseline CVLs were collected from participants in the Phase I PC-1005 trial before gel application using 10% of saline and pooled. Viability of ectocervical tissue after immersion in medium containing a 1:2 dilution of CVLs (three explants per condition) 18h was tested by MTT assay (OD595 of the formazan product was measured and normalized by the dry weight of the explants). Each symbol indicates an individual donor and the Mean±SEM of the LogOD595/g of tissue for each condition is shown. Log-normalized general linear mixed models were used for statistical analysis. Significant p-values of <0.001 (*** *) are indicated.

RESULTS (CON’T)

- CVLs were spiked with 500 TCID50 of HIV-1BaL, or 500 TCID50, HIV-1BaL, and 104 pfu HSV-2 per explant (three explants per condition) for 18h. Following washout, tissues were cultured and infections analyzed by HIV gag qRT-PCR and HSV-2 pal qRT-PCR in culture supernatants (three experimenters). Tissue viability was assessed by OD595 at 0h as well as at 24h post gel application. CVLs were spiked with 1:2 dilutions of CVLs to show (A) single challenge model; B) co-challenge model and C) CG co-challenge model concentrations in diluted CVLs are shown (Mean values of n = 1 - 4 experiments). CVLs do not inhibit HIV-1BaL infection in explants in a dose-dependent manner.

- Tissues were incubated with paired 1:2 dilutions of CVLs (baseline and post gel) for 4h, washed and then challenged with 500 TCID50 HIV-1BaL or 500 TCID50, HIV-1BaL, and 104 pfu HSV-2 per explant (three explants per condition) for 18h. Following washout, tissues were cultured and infections analyzed by HIV gag qRT-PCR and HSV-2 pal qRT-PCR in culture supernatants. CVL concentrations (Mean values of n = 1 - 4 experiments).

- MV-150 concentrations in CVLs inversely correlated with HIV-1BaL infection in the tissues in the single challenge model (p<0.0001) and co-challenge models (p=0.05). With every 10 ng/ml increase of MV-150, HIV-1BaL infection decreased by 95% and 85% in the single and co-challenge models, respectively. Infection inhibition was significant in the 4h but not in 24h post gel group vs. baseline (p<0.01) in the single challenge model. This was not the case in the co-challenge model.
- CG concentrations in CVLs inversely correlated with HSV-2 infection (p=0.01), resulting in a 30% decrease of HIV-2 infection at 100 ng/ml increase of CG. No significant differences between 4h and 24h groups vs. respective baselines were detected.

CONCLUSION

- Infections levels in the explants inversely correlated with MV-150 concentrations (HIV-1) and CG (HSV-2) in the CVLs.
- Overall, our data demonstrate the potential anti-HIV and anti-HSV-2 activity of PC-1005 in mucosal targets and endorse the further development of PC-1005 as a broad spectrum on-demand microbicide.

REFERENCE


FOR MORE INFORMATION

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