Distinct Pharmacodynamic Activity of Rilpivirine in Mucosal Explant Tissue

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Introduction

- Rilpivirine (RPV) is a potent, second-generation nonnucleoside reverse transcriptase inhibitor.
- A long-acting (LA) formulation has been developed for treatment and is being considered for HIV prevention.
- Two dose escalation clinical trials have been completed in men and women.
- SSAT040 evaluated 300 mg, 600 mg, and 1200 mg of RPV LA; men were dosed with 600 mg only.
- MWR1-01 evaluated 600 mg and 1200 mg of RPV LA and incorporated the ex vivo challenge assay.
- Drug penetration into rectal tissue (93 and 78 ng/ml) was approximately twice as much as compared to vaginal tissue (38 and 38 ng/ml) in both studies for the 600 mg dose.
- Significant suppression of HIV infection was noted 1 month post-injection for rectal tissue, but not for cervical or vaginal tissue (ex vivo challenge assay) in participants receiving the 600 and 1200 mg doses in MWR1-01.
- Our interest was to define the concentration of RPV (pharmacokinetics [PK]) needed to prevent HIV infection (pharmacodynamics [PD]) in mucosal tissue.

Methods

- RPV was supplied by Janssen Pharmaceutica, Belgium.
- HIV-1a9 was used for the experiments here and is the same virus used for the ex vivo challenge assay in MWR1-01. The 50% tissue culture infectious dose (TCID50) was determined in peripheral blood mononuclear cells.
- The in vitro 90% effective concentration (EC90) and 90% cytotoxic concentration (CC90) of RPV for HIV-1a9 was determined by the 4-parameter Emax model [(y = min + (max-y0)/(1+((x/EC90)^-Hillslope)))] (SigmaPlot11, Systat Software, Inc., San Jose, CA) using Tzan-bl assay data.
- For drug efficacy, 10-fold dilutions of RPV were applied to the basolateral chamber of polarized tissue explants for 24 h followed by infection with HIV-1a9 (5x10^4 TCID50 per explant for ectocervical tissue and 1x10^4 TCID50 per explant for colonic tissue) added to the apical surface for an additional 24 h. The explants were washed and supernatant was collected and replenished every 3-4 days for 21 days. HIV infection was measured in the supernatants by HIV p24 ELISA.
- In some experiments, explants were set up in quadruplicate and the second set of explants were collected after 48 h of culture for drug quantification using a validated LC-MS/MS method. Rilpivirine concentrations below the level of quantification (BLQ) were imputed to half the lower limit of quantification (LOQ).
- Importantly, the data presented here suggest that the concentrations of RPV in the rectal tissue exceeded by ~5-fold what would be needed to suppress viral infection (>16 ng/ml), but was 2.5-fold consistent with the PK data from the two clinical trials.

Conclusions

- RPV was effective in vitro against HIV-1a9 as measured in Tzan-bl and mucosal tissue assays.
- RPV penetrated colorectal tissue better than ectocervical tissue by >10-fold in vitro, which was consistent with the PK data from the two clinical trials.
- SSAT040 (600 mg) and MWR1-01 (600 mg) studies demonstrated similar concentrations of RPV in rectal (93 and 78 ng/ml) and vaginal (39 and 38 ng/ml) tissues.
- Importantly, the data presented here suggest that the concentrations of RPV in the rectal tissue exceeded by ~5-fold what would be needed to suppress viral infection (>16 ng/ml), but was 2.5-fold below the suppressive levels needed in cervical / vaginal tissue (>99 ng/ml).
- This was confirmed by the ex vivo challenge data from MWR1-01; HIV infection was suppressed in rectal tissue but not in cervical / vaginal tissues.
- Our data suggest that after parenteral dosing, sufficient levels of RPV appear to be present in the colon, but higher concentrations may be needed in the cervix / vagina for protection against HIV acquisition.

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References