Rectal Compartment Pharmacodynamics

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HIV and the Gut

McGowan I and Kotler DP unpublished data 1995
Introduction

- Rectal pharmacodynamics (PD) assays
- Rectal PD data from completed studies
  - HIV-1 p24
  - Molecular assays
- Lessons learned and questions for the future
Rectal Pharmacodynamic Assays

- Explant infection
  - *In vitro, ex vivo / in vitro* infection
  - Surgical tissue or endoscopic biopsies
  - Polarized or non-polarized assays
  - Choice of virus
  - Supernatant HIV-1p24
  - Supernatant RNA, explant RNA/DNA

- Rectal fluid PD
Explant Standardization

- Multisite comparison of anti-human immunodeficiency virus microbicide activity in explant assays using a novel endpoint analysis

- Key recommendations
  - Use of standardized endpoints
  - Drugs and/or virus reagents are centrally sourced
  - The same explant tissue and method used

Studies with Rectal PD

- **RMP-01**
  - UC781 gel (Phase 1)

- **RMP-02 / MTN-006**
  - TFV gel & oral (Phase 1)

- **CHARM-01**
  - TFV gel (Phase 1)

- **MWRI-01**
  - Rilpivirine LA

- **Ipergay**
  - Oral TDF/FTC

- **MTN-017**
  - TFV gel/oral (Phase 2)

- **CHARM-03**
  - Maraviroc gel & oral (Phase 1)

- **HPTN-069**
  - Oral TFV, MVC, FTC (Phase 2)
Population

- HIV-negative (N=36)

Center(s)

- Single

Sampling

- Colon
- 10 cm and 30 cm
- BL, post single dose, and post seven doses

Products (1:1:1)

- UC781 gel (0.1%)
- UC781 gel (0.25%)
- HEC placebo

Explant infection

- 10 cm and 30 cm
- HIV-1\textsubscript{BaL}
- \(10^4\) and \(10^2\) TCID\textsubscript{50}
- Cumulative D14 p24
- No PK/PD data

RMP-01 Results

- Infection rates at Baseline
  - HIV-1_{BaL} (10^4 TCID_{50}): 35/36 (97%)
  - HIV-1_{BaL} (10^2 TCID_{50}): 22/36 (61%)

- No difference in infection rates between 10 cm and 30 cm explants

- Significant suppression with single dose of UC781 0.25% gel

- No suppression seen with 7 daily (self administered) doses
RMP-01

RMP-02 / MTN-006

- **Population**
  - HIV-negative (N=18)

- **Center(s)**
  - 2 sites
  - Samples shipped to UCLA for analysis

- **Sampling**
  - Colon (15 cm)
  - BL, post single dose, and post seven doses; 30 min + Days 1-3, 4-6, 7-9, 10-12

- **Products (2:1)**
  - TFV gel (1%)
  - HEC placebo

- **Explant infection**
  - 10 cm and 30 cm
  - HIV-1$_{\text{BaL}}$
  - $10^4$ TCID$_{50}$
  - Cumulative D14 p24
  - PK/PD data

Anton PA et al. AIDS Res Hum Retroviruses 2012
RMP-02/MTN-006 Study Design
Single dose data (p = NS)

Anton PA et al. AIDS Res Hum Retroviruses 2012

7 daily gel doses data (p = 0.02)
CHARM-01

- **Population**
  - HIV-negative (N=14)

- **Center(s)**
  - 2 centers
  - Samples shipped to Pittsburgh

- **Sampling**
  - Flex sig (15 cm)
  - BL, and post 7D of each formulation

- **Products (crossover)**
  - TFV gel (1.0%)
  - RG TFV gel (1.0%)
  - RS TFV gel (1.0%)

- **Explant infection**
  - 15 cm
  - HIV-1_{BaL}
  - $10^4$ TCID$_{50}$
  - Weight adjusted cumulative D14 p24

PK/PD data

CHARM-01 Explant Data

Baseline
RF
RGVF
HEC/VF

P = 0.0001
P = 0.0008
P = 0.0024
P = 0.0001

Day 14 Log10 cumulative HIV-1 p24

Baseline
RF
RGVF
HEC/VF

Formulation

MWRI-01 / Single Dose

- **Population**
  - HIV-negative (N=36)

- **Center(s)**
  - 1 center

- **Sampling**
  - Flex sig (15 cm)
  - Cervicovaginal tissue
  - BL, and +1, 2, 3, 4, 5, 6 months after IM injection

- **Products (1:1)**
  - Rilpivirine LA 1200 mg
  - Rilpivirine LA 600 mg

- **Explant infection**
  - 15 cm
  - HIV-1_BaL
  - $10^4$ TCID$_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

McGowan I et al. HIV R4P 2014
MWRI-01 SD Explant Data

Dose Effect $P = 0.0009$
Visit Effect $P < 0.0001$
Dose*Visit Interaction $P = 0.2131$

McGowan I et al. HIV R4P 2014
Ex Vivo HIV-1 Infection of Rectal Biopsies

- Four biopsies obtained prior and after treatment (30 min, 1h, 2h, 4h, 8h, and 24h) biopsies gently disrupted with a small disposable pestle.
- 50 ng p24 of the R5-tropic HIV-1 reference strain NL-AD8 were added. Twenty hours after exposure to virus, the cells were treated with trypsin-EDTA to inactivate residual extracellular virus.
- The cell pellet was resuspended in medium containing 100U IL-2 and $5 \times 10^5$ MT4-R5 cells and cultured over an 8 day period. Supernatants were collected every day between day 3 and day 8, and at days 9, 10 or 11. ELISA p24 (Innotest, Ingen)
Ex Vivo HIV-1 Infection of Rectal Biopsies

- 10 participants had biopsies assessable at both time points with 4 biopsies per time point and per participant
- Before drug intake all participants had at least 1 biopsy infected (10/10) vs 6/10 after drug intake (p<0.07, MacNemar test for clustered data)
- Using a quantitative infectivity score (0: no infection to 6: infection detected at D4) median difference of mean scores: 1.38 (IQR: 0.25 -1.75), p<0.07, Wilcoxon sign rank test)
- Trend towards partial protection of rectal biopsies from HIV-infection after intake of a double-dose of TDF/FTC
- Need for additional post-exposure doses
Ongoing Studies
MWRI-01 / Multiple Dose

- **Population**
  - HIV-negative (N=12)

- **Center(s)**
  - 1 center

- **Sampling**
  - Flex sig (15 cm)
  - Cervicovaginal tissue
  - BL, and +1, 2, 3, 4, 5, 6 months after IM injection

- **Product**
  - Rilpivirine LA 1200 mg
  - IM x 3 every 2 months

- **Explant infection**
  - 15 cm
  - HIV-1\textsuperscript{BaL} / Clade C
  - $10^4 \mathrm{TCID}_{50}$
  - Weight adjusted cumulative D14 p24
  - PK/PD data

McGowan I et al. HIV R4P 2014
MTN-017

- Phase 2 expanded safety rectal microbicide study
- Crossover design with 8 week dosing periods
  - Oral TDF
  - Topical TFV gel daily
  - Topical TFV gel with sex
- Tissue substudy (N=36)
  - Bangkok
  - Pittsburgh

- Assays
  - Compartmental PK
  - Explant infection
  - Rectal fluid PD
- BL & end of each dosing period
- Explant infection
  - 15 cm / HIV-1$_{BaL}$
  - $10^4$ TCID$_{50}$
  - WA D14 HIV-1 p24
HPTN-069

- Phase 2 comparison of four oral PrEP regimens
- N = 600
- 48 week exposure with 1 week washout period
- Treatment arms:
  - MVC
  - MVC + FTC
  - MVC + TDF
  - FTC + TDF

- Sample collection
  - BL, +24, +48, +49 weeks

- Tissue substudy
  - N = 120
  - Rectal and cervical

- Explant infection
  - 15 cm / HIV-1BaL
  - $10^4$ TCID$_{50}$
  - WA D14 HIV-1 p24
HPTN-069 Single Site Data

Explant Viral Load

Baseline | Week 24 | Week 48 | Week 49

-1000 | 0 | 1000 | 2000 | 3000 | 4000
CHARM-03

- **Population**
  - HIV-negative (N=19)

- **Center(s)**
  - Single center

- **Sampling**
  - Flex sig (15 cm)
  - BL, and post 7D of each formulation

- **Products (crossover)**
  - Oral MVC
  - Rectal MVC gel
  - Vaginal MVC gel

- **Explant infection**
  - 15 cm
  - HIV-1_{BaL}
  - 10^4 TCID_{50}
  - Weight adjusted cumulative D14 p24
  - PK/PD data

CHARM-03 Design

Female Participants (N = 9)

Rx 1  Rx 2  Rx 3

Screen Female Participants
Enroll F: N=9  R. Bx = 9  CV Bx = 9
Initiate Oral MVC
Day 8 R. Bx (N=9)  CV Bx (N=3)
Initiate Rectal MVC
Day 9 CV Bx (N=3)  R. Bx (N=3)
Day 10 CV Bx (N=3)  R. Bx (N=6)
Initiate Vaginal MVC
Day 9 CV Bx (N=3)  R. Bx (N=3)
Day 8 R. Bx (N=9)  CV Bx (N=3)
Day 10 CV Bx (N=3)  R. Bx (N=6)

14-21 day recovery period

Rx= Treatment; F= Female; R= Rectal; Bx= Biopsies & CV= Cervical; N = number of participants having rectal or cervical biopsies
Participants will be randomized to product sequence and mucosal sampling schedule at Visit 2 (Enrollment)
MTN-033 (Adonis) Study

- Phase 1 PK assessment of single dose TFV and dapivirine (DPV) gels
- N = 24
- Gels delivered by application or by digital/phallic insertion

- Compartmental PK
- Rectal fluid PD
- Explant infection
  - 5 cm & 15 cm
  - HIV-1\textsubscript{BaL}
  - 10\textsuperscript{4} TCID\textsubscript{50}
  - Weight adjusted cumulative D14 p24

In Development
Molecular Assays
Molecular Assays

- Cumulative Day 14 HIV-1 p24 routinely used to quantify explant infection but has some limitations
  - Explant need to be cultured for 2 weeks
  - Assay sensitivity limited
  - Samples may need to be diluted for quantification

- Quantification of HIV-1 nucleic acids in supernatant and tissue is an alternative
Molecular Assay Study

- Goal was to determine whether molecular assays provide a more sensitive approach to the quantification of explant infection
- Explants collected from 8 healthy volunteers and challenged with HIV-1_{BaL} or HIV-1_{CHO77}
- Supernatant and tissue harvested over 14 day period
Tissue Viral Kinetics

Janocko L et al. AIDS Res Hum Retroviruses 2015
Supernatant Viral Kinetics

Janocko L et al. AIDS Res Hum Retroviruses 2015
Lessons Learned
Lessons Learned

- Ex-vivo / in vitro explant studies are now being used to characterize antiretroviral efficacy in multiple PrEP studies.
- Assay performance improved by using standardized assays, endpoints, and viral stocks.
- Explant viral kinetics vary according to the virus used.
Future Questions
Future Questions

- What is the role (if any) of molecular assays in characterizing explant infection?
- What is the most relevant virus to use in explant infection studies?
- Can resistant virus replicate in explant tissue?
- Would MMC challenge studies diminish assay variability?
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