Evidence supporting Liver Targeting of Tenofovir Exalidex (TXL)

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INTRODUCTION

Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor indicated for the treatment of HIV and HBV. Tenofovir is administered as a pro-drug, as TFV itself is not absorbed after oral administration. Administration of the first commercially available pro-drug of TFV, tenofovir disoproxil fumarate (TDF) results in high systemic exposures of TFV while conferring clinical benefit. However, these high TFV levels have been associated with renal and bone toxicities. A second commercially available pro-drug, tenofovir alafenamide (TAF), results in significantly reduced TFV exposures and has fewer renal and bone implications, while maintaining efficacy. Tenofovir exalidex (TXL) is a novel pro-drug of TFV designed specifically to target liver to allow for antiviral efficacy in chronic HBV patients and to minimize off-target effects. Herein, we describe evidence of liver targeting of TXL in animal models and humans.

**Premise:** “Lipid” tail chemically modified tenofovir designed to target liver

TXL is designed to mimic lysophosphatidylcholine to take advantage of natural lipid uptake pathways and achieve high hepatic intracellular concentrations, while minimizing high circulating levels of TFV

**TXL targets liver in an animal model**

Double cannula model results in 86% extraction rate of TXL by liver.

**TXL lowers viral load in animal model**

TXL dosed at 10 mg/kg/day lowers HBV transgenic mouse model hepatic viral load by 97%.

**TXL 50 mg PK in HBV + MAD study**

No statistically significant differences amongst groups in Phase 2a

**Antiviral efficacy of TXL in HBV + MAD study**

Hepatitis B Patients Study CTRV-CMX-201

**PK model to demonstrate TXL liver targeting**

Pharmacokinetic Physiologic Modeling of Hepatic Clearance

Many models of hepatic clearance exist, including:
- Well-stirred
- Tube
- Distributed
- Dispersion
- Tank-in-series

Models yield similar output(s), except at “extremes” of either extremely low or high extraction ratios

**Pharmacokinetic Physiologic Modeling (continued)**

Oral Clearance (Cl/F) = Hepatic Clearance (ClH), for drugs with high intrinsic clearance, ClH

\[ F = \frac{C_{\text{oral}}}{C_{\text{Hep}}} \times \frac{f_{\text{a}}}{C_{\text{Hep}}} \times \text{F} \] (represents a hybrid)

F is comprised of pharmacological formulation and PK/PD parameters

Well-Stirred Model

- \( CL_{\text{H}} = \frac{Q_{\text{H}} \cdot E_{\text{H}}}{Q_{\text{H}} + f_{\text{u}} \cdot CL_{\text{H}} \text{inst}} \)
- \( E_{\text{H}} = \frac{f_{\text{u}} \cdot CL_{\text{H}} \text{inst}}{Q_{\text{H}} + f_{\text{u}} \cdot CL_{\text{H}} \text{inst}} \)
- \( CL_{\text{H}} = Q_{\text{H}} \left( \frac{f_{\text{u}} \cdot CL_{\text{H}} \text{inst}}{Q_{\text{H}} + f_{\text{u}} \cdot CL_{\text{H}} \text{inst}} \right) \)

Well-stirred model serves to illustrate parameters that influence hepatic clearance for highly extracted drugs

**Pharmacokinetic Physiologic Modeling (continued)**

Alterations to hepatic blood flow result in PK better dynamics

**TXL in Healthy Volunteers: Fasted vs Fed**

- Normal hepatic blood flow = 1.5 – 1.8 L/min
- Prodrug (TXL):
  - AUC, Fasting versus Fed: –34% reduced
- Metabolite (TFV):
  - AUC, Fasting versus Fed: –35% increased
- Postprandial hepatic blood flow can increase by 36%-69% (Clinical Pharmacology & Therapeutics 34(5) 516-23 – October 1983)

**CONCLUSIONS**

- TXL’s lipid tail confers liver targeting
- Double cannulated rat model demonstrated high hepatic extraction
- Animal efficacy model and HBV infected patients both indicate TXL has effect on liver
- PK modeling demonstrates that hepatic clearance is dependent on hepatic blood flow for drugs that target the liver, including TXL
- An alteration to hepatic blood flow, induced by food, demonstrates a corresponding and observed alteration to the PK profile in HBV subjects
- Development of highly extracted (hepatic) drugs offer opportunities to boost efficacy by:
  1. Optimizing formulation (drug loading to portal circulation)
  2. Altering hepatic blood flow