HEP DART 2017

frontiers in drug development for viral hepatitis

Evidence supporting Liver Targeting of Tenofovir Exalidex (TXL)

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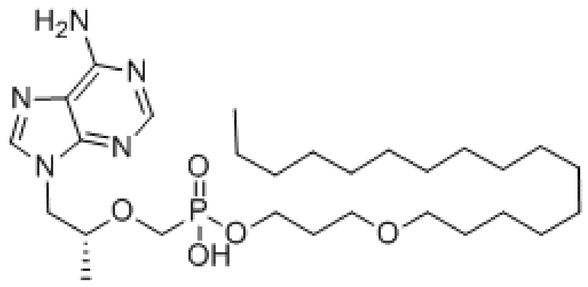
INTRODUCTION

Tenofovir (TFV) is a nucleotide reverse transcriptase inhibitor indicated for the treatment 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.

Tenofovir Exalidex (TXL)

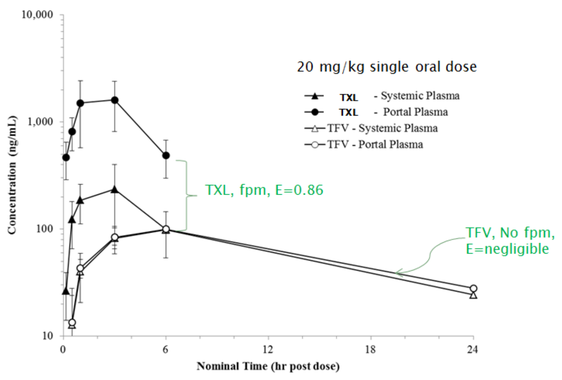
Premise: "Lipid" tail chemically modified tenofovir designed to target liver



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

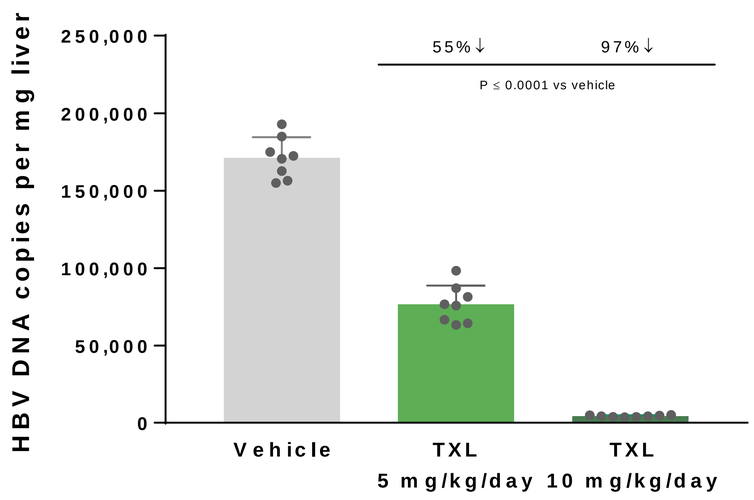
TXL targets liver in an animal model

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



❖ TAF, E=0.65 (dog) (*Mol. Pharmaceutics, **2013**, 10(2), 459–466*)

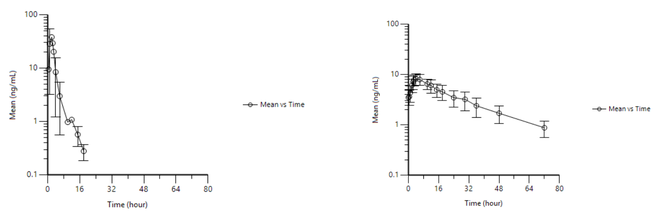
TXL lowers viral load in animal model



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

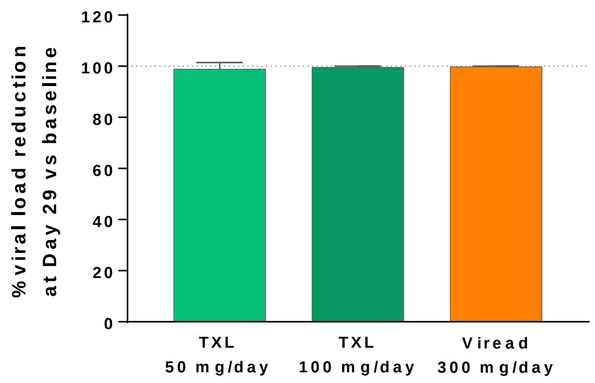
Study CTRV-CMX-201- TXL 50 mg dose



Antiviral efficacy of TXL in HBV + MAD study

Hepatitis B Patients Study CTRV-CMX-201

No statistically significant differences amongst groups in Phase 2a



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 (Cl_H), for drugs with high intrinsic clearance, Clint')
$F = f_{disintegration} \times f_{dissolution} \times f_{gut} \times f_{liver}$ (represents a hybrid)
F is comprised of pharmaceutical formulation and PK/PD parameters

Well-Stirred Model

$$CL_H = Q_H \cdot E_H$$
$$E_H = \frac{f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$$
$$CL_H = Q_H \left(\frac{f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}} \right)$$

- Q_H, hepatic blood flow
- F_u, unbound fraction
- Cl_{int}, intrinsic clearance
- CL_H, hepatic clearance
- E_H, hepatic extraction ratio

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

The Clearance of Highly Extracted Drugs is Determined by Hepatic Blood Flow

$$CL_H = Q_H \cdot E_H$$
$$E_H = \frac{f_u \cdot CL_{int}}{Q_H + f_u \cdot CL_{int}}$$
$$f_u \cdot CL_{int} \gg Q_H$$
$$CL_H = Q_H \left(\frac{f_u \cdot CL_{int}}{f_u \cdot CL_{int}} \right)$$
$$CL_H = Q_H$$

Relative to Q_H, Cl_{int} plays a minor role and can be disregarded

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(3):316–23 · 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