Incorporation Into Lipid Nanoparticles Extends the Duration of Activity of Treprostinil in an Acute Hypoxia Rat Model of Pulmonary Arterial Hypertension

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Inhaled treprostinil extended vasodilatory effect as compared with TRE

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INTRODUCTION

- Treprostinil (TRE) is a prostacyclin analogue used to treat pulmonary arterial hypertension (PAH).
- In this study, we designed a TRE delivery system based on the development of a lipid nanoparticle (LNP) suspension for the encapsulation and sustained release of drugs.
- Uniform, sonicated treprostinil lipid nanoparticles (TRE-LNPs) were composed of (i) TRE, (ii) a cationic lipid to counteract the negatively charged phospholipid and to physico-chemically stabilize the core of the nanoparticles, (iii) a hydrophobic “filler” to stabilize the core of the particle, and (iv) a nominal concentration of phosphatidylcholine to offset the hydrophilic lipid to the LNP nanoparticles.

METHODS

TRE-LNP Production

- Solvent flash precipitation via microaerobic flash drying was used for the one-step, continuous-flow synthesis of uniform sonicated TRE-LNPs (Figure 2).
- In this process, a core of alkylated-treprostinil and lipid is impregnated with aqueous cationic peripheral to the TRE strain.
- As the aqueous streams meet with and laterally focus the miscible-solvated lipid stream, the organic and aqueous phases interfacialize, producing a solvent composition in which the lipid is increasingly less soluble.
- This causes the lipid to self-assemble into intermediate aggregates that eventually close themselves into spherical nanoscale LNPs.

AIMS

- To design an inhalable TRE formulation for the treatment of PAH that would have an improved pharmacokinetics (PK) profile relative to the current inhalated TRE therapy for PAH Tyvaso®
- To formulate a once-daily dosing schedule
- To achieve this, we developed a treprostinil TREC vehicle with an optimized drug payload and inhalation profile to support a sustained vasodilatory response relative to free TRE.

RESULTS

In Vitro TRE-LNP Characterisation Methods

- Rat model of PAH
- Male Syrian hamster lungs were cannulated, artificially ventilated and prepared for measurement of mean pulmonary arterial pressure (mPAP), mean systemic blood pressure (mSAP), heart rate (HR), and arterial oxygen saturation (SaO2).
- Pulmonary vasodilatory activity of the delivered TRE-LNP was measured by the decrease in mPAP (% Hypoxic Baseline Level) and the increase in activation relative to the control samples was calculated.
- In the hypoxic rat model, the pulmonary vasodilatory activity of inhaled TRE-containing LNPs, was extended beyond that of treprostinil TRE in solution, which is consistent with an extended PK profile of the drug, observed in excised blood plasma.
- Packaging TRE into a nanoparticle formulation increased duration of the vasodilatory effect relative to the drug-free tissue, but did not sufficiently in a one-day during schedule based on the pharmacokinetic profile observed.
- To further improve nanoparticle retention of TRE, we developed a derivatized TRE agonist made by covalent attachment of alkyl chains (used for LNP drugs by Lübbe and ERS Poster #2358). We believe that this approach will result in a sustained vasodilatory response well beyond that observed with TRE-LNPs and inhaled drug.
- Please see other posters in this series:
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