Preventing Duchenne Muscular Dystrophy Cardiomyopathy Through Antagonism of the Thromboxane Prostanoid Receptor: An FDA Funded Phase 2 Clinical Trial

Larry W. Markham¹, Jonathan H. Soslow², Erica J. Carrier³, James D. West³, Jerry Fox⁴, Leo Pavliv⁴ and Ines Macias-Perez⁴

¹Division of Cardiology, Department of Pediatrics, Riley Children’s Hospital, Indianapolis, IN; ²Division of Cardiology, Department of Pediatrics, Vanderbilt University Medical Center (VUMC), Nashville TN; ³Division of Allergy, Pulmonary, and Critical Care, Department of Medicine, VUMC, Nashville TN; ⁴Cumberland Pharmaceuticals Inc., Nashville, TN

BACKGROUND

- Muscular dystrophy (MD) is associated with mechanical damage and increased membrane permeability of muscle cells. In the heart, this causes progressive weakness and cardiac fibrosis in Duchenne (DMD).
- Isoprostanes, products of oxidative stress, are increased in DMD and can signal through the thromboxane/prostanoid receptor (TPR) to cause fibrosis. TPR activation increases calcium levels inside the heart muscle cells and could contribute to arrhythmia or heart damage in DMD.
- We thus hypothesized that TPR activation contributes to the cardiac phenotype of DMD, and that blocking the TPR would be cardioprotective in mouse models of MD.

MOUSE MODELS

- DMD mouse models:
  - Utrophin/dystrophin double knockout (DKO)→Evaluated at 10 weeks of age
  - 2nd generation dystrophin/RNA telomerase component double knockout (mdx/mTR), which has shortened telomeres→Evaluated at 6 months of age, with a midpoint echo at 3 months
- Limb-girdle muscular dystrophy (LGMD) mouse model: Delta-sarcoglycan knockout (dSG)→Evaluated at 3 and 6 months of age.

Mice were given either normal drinking water, or water containing 25 mg/kg/day of the TPR antagonist ifetroban, beginning at weaning. Water and drug changed 1x/week.

PRECLINICAL DATA

**Ifetroban prevents cardiac fibrosis and improves survival in DMD mice**

Treatment with the TPR antagonist ifetroban (If) improves survival (A), normalizes fractional shortening and ejection fraction (B) and decreases epicardial intimal fibrosis (C; n=6) in dSG KO LGMD male mice. Fibrotic area was quantified from trichrome-stained whole slices in Leica Image Analysis using the same trichrome-defined mask image for all slides. We also decreased phospho-Smad2/3 (D), a TGF-β signaling molecule (D; n=2). Comparison by unpaired t-test; intervening lanes were removed from blot in D. Utrophin-dystrophin double knockout DMD mice (DKO) and dystrophin KO mice with short telomeres (G2 mdx/mTR) have increased survival (E, G) and improved LV cardiac index with ifetroban treatment (F, H). The results of log-rank test (F, H) comparisons are shown. (H) is male mice only, due to sex differences of cardiac output in fully grown mice.*, p<0.05 by log-rank test. dSG KO = delta-sarcoglycan knockout.

CENTRAL HYPOTHESIS

Our preclinical studies demonstrate ifetroban is cardioprotective in several muscular dystrophy models of heart disease.

These data have led us to design the proposed randomized, placebo-controlled, multicenter phase 2 trial to test the central hypothesis that Thromboxane Receptor signaling contributes to cardiac inflammation and thus treatment with ifetroban will impact heart muscle disease in DMD patients.

TRIAL DESIGN

- 48 DMD participants
  - ≥ 7 years of age
  - Stable or No steroids allowed
  - EF ≥ 35% by MRI/Echo
  - ACEI, BB & ARB allowed
  - Aldosterone receptor antagonists & exon-skipping agents allowed

**Ifetroban**

- 12 months of treatment
- 48 DMD participants needed ≥ 7 years of age
- Office visits
- 3 Months of treatment

The FIGHT DMD Clinical Trial will determine the safety, pharmacokinetics and efficacy of ifetroban in Duchenne muscular dystrophy.

Ifetroban is being studied as a potential anti-fibrotic medication in several diseases but is not approved for and has never been studied in DMD.

Ifetroban is a treatment thought to impact the heart disease associated with DMD.

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