Pharmacodynamic Effects of a Single Dose of CK-3773274 in Cats with Hypertrophic Cardiomyopathy

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ABSTRACT

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy in the absence of known causes. HCM can be due to genetic mutations that affect sarcomeric proteins, leading to myocardial hypercontractility. HCM is often complicated by left ventricular outflow tract obstruction (LVOTO) and patients may be at greater risk of cardiovascular death. Medications targeted to address the pathophysiology of HCM and ameliorate LVOTO are needed. CK-3773274 (CK-274) is a novel, small molecule cardiac myosin inhibitor that reduces myocardial contractility *in vitro* and *in vivo*. Cats have naturally occurring HCM commonly complicated by LVOTO and are an excellent large animal model for investigation of HCM therapeutics. In this study, we aim to characterize the pharmacodynamic effect of a single oral dose of CK-274 on cardiac function in cats with hypertrophic cardiomyopathy and LVOTO.

Methods

Eight purpose-bred cats with naturally occurring HCM and LVOTO due to the A31P mutation in cardiac myosin binding protein C (cMyBP-C) were included in a randomized, controlled, crossover study. Cats were randomized to receive vehicle, 0.3 mg/kg, or 1 mg/kg CK-274 treatment, and received echocardiograms at baseline, 6, 24, and 48 hours post-treatment. All cats were crossed over to all treatment groups.

Results

CK-274 (1 mg/kg) reduced mean left ventricular (LV) fractional shortening at 6, 24, and 48 hours post-treatment (mean reduction 13.6%, $p = 0.03$; 15.4%, $p = 0.01$; 11.6%, $p = 0.02$, respectively). CK-274 (1 mg/kg) increased LV systolic internal dimension at 6 and 24 hours post-treatment (mean increase 0.21 cm, $p = 0.046$; 0.25 cm, $p = 0.03$), and did not affect LV diastolic internal dimension. Left ventricular outflow tract (LVOT) peak pressure gradient was reduced with CK-274 (0.3 mg/kg) treatment (median pressure gradient at baseline 27.1 mmHg [interquartile range {IQR} 18.3–33.3] vs 24 hours post-drug, 7.3 mmHg [IQR 14.2–19.7], $p = 0.01$). Heart rate did not change for any treatment group over time. No differences were noted following vehicle administration at any time point.

Conclusion

In HCM-affected cats with the cMyBP-C A31P mutation, the cardiac myosin inhibitor CK-274 is well tolerated at the studied doses and caused dose-related changes in LV systolic function and reductions in LVOT peak pressure gradient.

INTRODUCTION

- Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy in the absence of known causes. HCM can be due to genetic mutations that affect sarcomeric proteins, leading to myocardial hypercontractility. HCM is often complicated by left ventricular outflow tract obstruction (LVOTO) and patients may be at greater risk of cardiovascular death. Medications targeted to address the pathophysiology of HCM and ameliorate LVOTO are needed
- CK-3773274 (CK-274) is a novel, small molecule cardiac myosin inhibitor that reduces myocardial contractility *in vitro* and *in vivo*
- Cats have naturally occurring HCM commonly complicated by LVOTO and are an excellent large animal model for investigation of HCM therapeutics. In this study, we aim to characterize the pharmacodynamic effect of a single oral dose of CK-274 on cardiac function in cats with hypertrophic cardiomyopathy and LVOTO

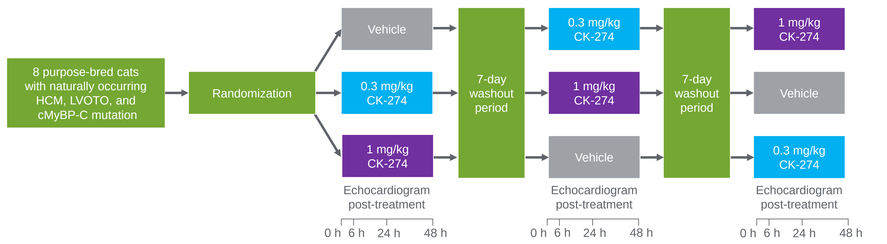
METHODS

Animals

- Eight purpose-bred cats with naturally occurring HCM and LVOTO due to the A31P mutation in cardiac myosin binding protein C (cMyBP-C) were included in a randomized, controlled, crossover study
- HCM was defined as maximal left ventricular wall thickness greater than 6 mm on a two-dimensional right parasternal short- or long-axis view; LVOTO was defined as a late-peaking spectral continuous wave Doppler signal with a velocity of > 1.9 m/s
- Normality was assessed using a D'Agostino and Pearson test. If parametric, data were analyzed using a repeated measures analysis of variance; if nonparametric, data were analyzed using a Friedman test

Study Design

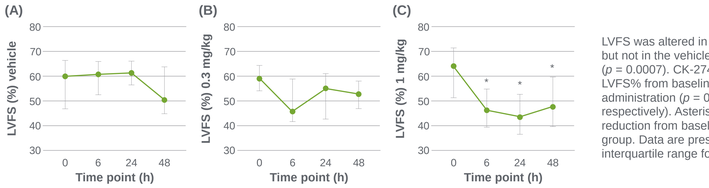
Schematic of *in vivo* crossover design



Cats were confirmed to have HCM via baseline complete echocardiogram. Cats were randomized to receive vehicle, 0.3 mg/kg, or 1 mg/kg CK-274 treatment, and received echocardiograms at baseline, 6, 24, and 48 hours post-treatment. Following each echocardiogram, blood samples were obtained to measure CK-274 plasma concentration. All cats were crossed over to all treatment groups. There was a washout period of 1 week between treatment groups.

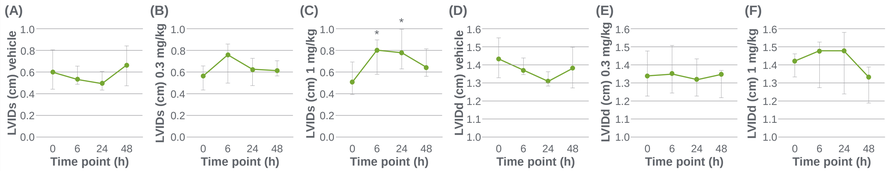
RESULTS

Left ventricular fractional shortening (LVFS) is displayed for (A) vehicle, (B) 0.3 mg/kg, and (C) 1 mg/kg treatment groups at baseline, 6, 24, and 48 hours post-CK-274 dosing



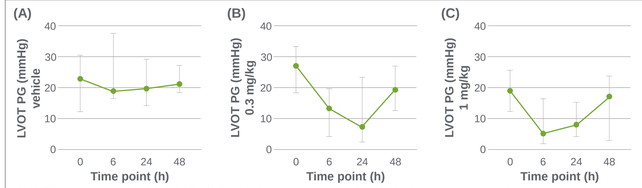
LVFS was altered in the 1 mg/kg treatment group but not in the vehicle group or 0.3 mg/kg group ($p = 0.0007$). CK-274 (1 mg/kg) significantly reduced LVFS% from baseline at 6, 24, and 48 hours post administration ($p = 0.03$, $p = 0.01$, $p = 0.02$, respectively). Asterisks denote significant ($p < 0.05$) reduction from baseline in the 1 mg/kg treatment group. Data are presented as median and interquartile range for each time point.

Left ventricular systolic internal dimension (LVIDs) and left ventricular diastolic internal dimension (LVIDd) at 6, 24, and 48 hours post administration of treatment. LVIDs: (A) vehicle, (B) CK-274 (0.3 mg/kg) and (C) CK-274 (1 mg/kg). LVIDd: (D) vehicle, (E) CK-274 (0.3 mg/kg) and (F) CK-274 (1 mg/kg)



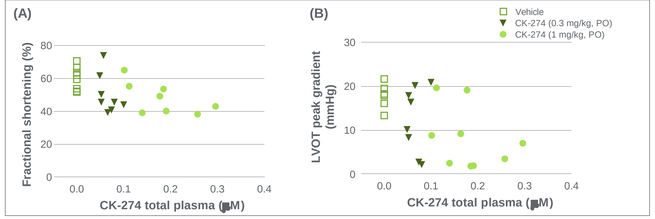
LVIDs was altered in the 1 mg/kg treatment group but not the vehicle group or 0.3 mg/kg group ($p = 0.006$). CK-274 at 1 mg/kg increased LVIDs from baseline at 6 and 24 hours post-treatment ($p = 0.046$, $p = 0.03$, respectively), but did not affect LVIDd in any treatment group. Asterisks denote significant ($p < 0.05$) increase from baseline in the 1 mg/kg treatment group. Data are presented as median and interquartile range for each time point.

Left ventricular outflow tract peak pressure gradient (LVOT PG) at 6, 24, and 48 hours post administration of treatment. (A) LVOT PG and vehicle, (B) LVOT PG and CK-274 (0.3 mg/kg), and (C) LVOT PG and CK-274 (1 mg/kg)



LVOT PG was reduced with CK-274 (0.3 mg/kg) treatment overall ($p = 0.01$). Data are presented as median and interquartile range for each time point.

Left ventricular fractional shortening (LVFS) and left ventricular outflow tract peak pressure gradient (LVOT PG) as a function of CK-274 plasma concentration at 6 hours post administration of treatment. (A) Individual cat LVFS and (B) LVOT PG tend to decrease with higher CK-274 plasma concentration



CONCLUSIONS

- In HCM cats with a cMyBP-C A31P mutation, the cardiac myosin inhibitor CK-274 is well tolerated at the studied doses and caused dose-related reductions in LV systolic function and LVOT peak pressure gradient
- Future studies in this feline model could further elucidate the utility of cardiac myosin inhibitors in obstructive hypertrophy cardiomyopathy

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Disclosures

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