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Chronic treatment with PB1046, a stable and long-acting vasoactive intestinal peptide receptor agonist, improves cardiac and skeletal muscle function in mouse models of Duchenne Muscular Dystrophy

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Introduction

Cardiac dysfunction is a frequent manifestation of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) and a common cause of death for individuals with these conditions. While the core aim for a cure for this disease is to target the cause of muscle degeneration (i.e., loss of dystrophin), treatments aimed at alleviating cardiomyopathy and preventing fibrosis in skeletal and cardiac muscle may represent valuable adjunct therapy.

PB1046 is a novel long-acting biopolymer-based selective VPAC2 receptor agonist comprising vasoactive intestinal peptide (VIP) fused to an elastin like polypeptide. PB1046 demonstrated positive lusitropic (relaxation) and inotropic (contraction) effects in both large and small animal models of heart failure. Furthermore, PB1046 has been shown to be safe and well tolerated with an extended half-life in single dose subcutaneous and single dose IV studies in human volunteers.

The objective of this study was to evaluate whether chronic administration of PB1046 in the setting of genetically-induced cardiac/muscular dystrophy (consistent with the clinical presentation of DMD patients) demonstrates cardio-protective effects and to examine its effect on skeletal muscle function.

Materials and Methods

MDX (C57BL10/ScSnDMD^{mdx}, dystrophin deficient, n = 21) and DKO (double knockout) *mdx/utrn-/-* (dystrophin/utrophin deficient, n = 13) mice were administered PB1046 (1.5 mg/kg) or 0.9% NaCl saline (control) subcutaneously three times a week for the duration of the study (32 weeks for MDX and up to 4 weeks for DKO). Left ventricular function (via echocardiography; ECHO) and electrocardiography (ECG) changes were monitored during routine check-ups. Terminal assessments included either an anesthetized preparation in an instrumented animal with a pressure catheter to measure systemic/left ventricular hemodynamics or skeletal muscle strength evaluation on the extensor digitorium longus (EDL) (MDX only). Tissue samples were flash frozen or fixed in formalin for histological assessments (Sirius Staining and Macrophage and CD counting).

Results

ECHO

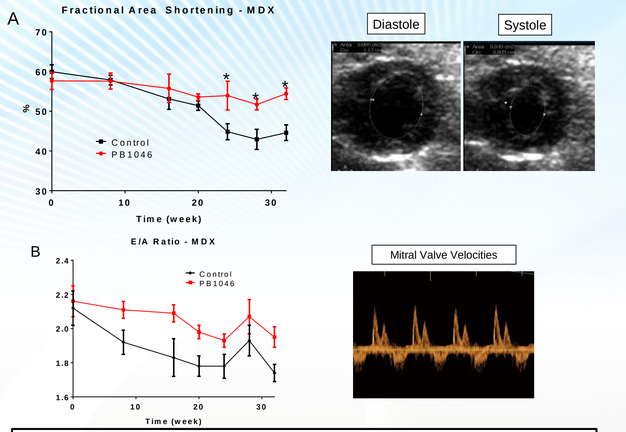

Fig 1. Cardiac function monitored via echocardiography. n = 10 - 11, *P< 0.05 vs controls

Chronic PB1046 slowed cardiac deterioration in MDX mice. The fractional area shortening (an index of systolic function) was preserved over the duration of the study (P<0.05). Ventricular filling velocities (E/A ratio – an index of diastolic function) tended to be faster throughout the study, but did not reach statistical significance.

Electrocardiograms were also assessed at these time points. Throughout the study, PB1046 treated MDX mice tended to have shorter QRS (preserved ventricular conduction) when compared to placebo-treated animals, but did not reach statistical significance (data not shown). Similar trends were noted in DKO mice, with PB1046 treatment appearing to blunt the QRS prolongation noted in controls (data not shown).

Terminal hemodynamics

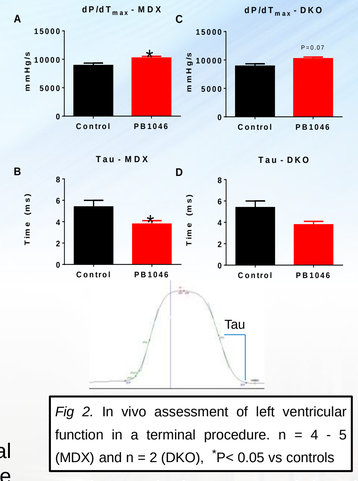

Fig 2. In vivo assessment of left ventricular function in a terminal procedure. n = 4 - 5 (MDX) and n = 2 (DKO), *P< 0.05 vs controls

In vivo analysis suggested that the elevated maximal rate of pressure rise (dp/dt$_{max}$ - an index of systolic function) was significantly greater and the Tau constant of relaxation was faster with PB1046 treatment in MDX mice (P<0.05).

Skeletal Muscle Physiology

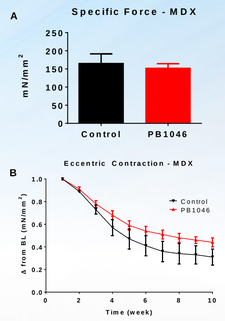

Fig 3. Skeletal muscle physiology was evaluated in isolated EDL. n = 4 – 16.

In evaluation of skeletal muscle function, PB1046 treatment protected against contraction-induced damage on isolated EDL muscles without changing specific force in MDX mice.

Collagen Content and Macrophage Count

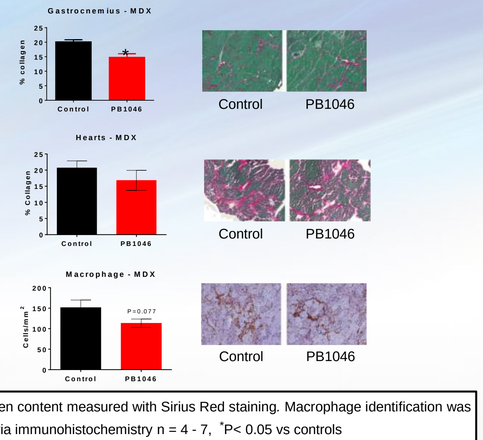

Fig 4. Collagen content measured with Sirius Red staining. Macrophage identification was determined via immunohistochemistry n = 4 - 7, *P< 0.05 vs controls

In agreement with increased skeletal and cardiac function, PB1046 significantly decreased the extent of fibrosis (collagen content) in the gastrocnemius muscle in the MDX mice (no significant effect in quad, diaphragm or tibialis anterior, though trends were evident). Additionally there was a trend to reduce collagen content in MDX heart muscle. Although n was small, similar trends in fibrosis were noted in DKO mice hearts (data not shown).

Although no differences were observed in immune cells (CD3, CD4, CD8, data not shown), total macrophage count trended to be lower with PB1046 treatment.

Conclusion

Chronic treatment with a novel VIP receptor agonist, PB1046, ameliorated DMD myopathy by slowing cardiac deterioration and protected against contraction skeletal muscle induced damage. In addition to positive inotropic and lusitropic effects on cardiac function, decreased fibrosis (collagen content) is likely to contribute to positive effects of PB1046 on both cardiac and skeletal muscle.

Disclosure: RL Hamlin, J Ballance, L Georgopoulos, S Arnold and CL del Rio have stock options in PhaseBio Pharmaceuticals, Inc.

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