Elevation of fast but not slow troponin I in the circulation of patients with Becker and Duchenne muscular dystrophy

Benjamin L Barthel PhD1, Dan Cox2, Marissa Barbieri3, Abby Bronson1, Michael Ziembas, Volker Straub1, Eric P. Hoffman2, Alan J Russell3

1Edgewise Therapeutics, BioFrontiers Institute, University of Colorado, Boulder, CO 80303, USA, 2The John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE1 3BZ, UK, 3Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, Binghamton University – State University of New York, Binghamton, NY 13902 USA contact: arussell@edgewise.com

BACKGROUND: One of the hallmarks of injured skeletal muscle is the appearance of elevated skeletal muscle proteins in circulation. Human skeletal muscle generally consists of a mosaic of slow (type I) and fast (type IIa, IIx/d) fibers, defined by their myosin isoform expression. Limited evidence suggests that muscle injury in healthy volunteers (HV) results in the appearance of muscle biomarkers from fast but not slow fibers in circulation (1). We sought to understand if this is also the case in Becker and Duchenne muscular dystrophy (BMD, DMD) by measuring troponin I isoforms from fast and slow skeletal muscle fibers in blood samples from patients.

METHODS, SAMPLES AND DEMOGRAPHICS: An ELISA that selectively measures fast and slow skeletal troponin I (TNNI2 and TNNI1) was used to measure a cross-section of patient plasma samples from healthy volunteers (N=50) and affected individuals. All samples were obtained according to local ethics policies. Plasma and serum for DMD patients (N=132) was received from the Newcastle MRC Centre Biobank for Rare and Neuromuscular Diseases. BMD samples were from a biomarker study at Binghamton University – SUNY (BMD, n=52). All samples were obtained with the appropriate patient consent.

RESULTS

Fast but not slow muscle TNNI is elevated in DMD and BMD

In DMD, Fast TNNI and CK decrease with age but not slow TNNI

DISCUSSION

• This is the first cross-sectional, retrospective study to describe differences between fast and slow skeletal muscle fiber biomarkers in DMD and BMD patient plasma
• Findings of differential troponin levels agree with previous studies of muscle injury after eccentric exercise in healthy volunteers (1)
• This appears to be distinct from muscle injury via sepsis or trauma where both fast and slow TNNI are elevated (2)
• Previous studies have demonstrated preferential fast fiber injury in DMD patients (3). Our data extend these findings to suggest that slow fibers do not appear to leak muscle proteins in the context of BMD/DMD
• The majority of healthy volunteers (83%) had TNNI2 levels below the lower level of detection of the ELISA (<0.1 ng/ml), while only 4% of BMD and 6% of DMD patients had non-measurable levels of TNNI2.
• This is in marked contrast to CK where large overlap exists, particularly in the setting of BMD or older DMD patients where plasma CK is commonly low

REFERENCES