Effects of Combined Enzyme Replacement Therapy and Simvastatin Treatment on Cervical Spine Intervertebral Disc Disease in Mucopolysaccharidosis I

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Disclosures:

Introduction: Mucopolysaccharidosis I (MPS I) is a lysosomal storage disorder characterized by deficient α-L-iduronidase activity, leading to the accumulation of poorly degraded dermatan and heparan sulfate glycosaminoglycans (GAGs) [1]. Clinical presentation includes significant cervical spine disease, leading to spinal cord compression and kypho-scoliosis [2], which presents a challenging hurdle for physicians seeking to improve the quality of life for MPS I patients [3]. Current treatment options for MPS I include bone marrow transplantation (BMT) and enzyme replacement therapy (ERT). However, both treatment modalities show limited efficacy in attenuating the orthopaedic tissue manifestations of the disease [4,5]. The diagnosis and subsequent administration of ERT often occurs as late as a decade after disease onset, thereby missing critical developmental stages of early growth, leaving the debilitating spine disease largely unimproved [4]. A previous study showed that the efficacy of ERT for improving spinal manifestations in MPS I was strongly dependent on the enzyme dose, the age at which treatment commenced and the delivery route (intravenous vs. intrathecal) [5]. In our previous work on MPS VII (beta-glucuronidase deficiency), we demonstrated that accelerated disc degeneration was associated with chronic inflammation and upregulation of destructive proteases [6]. Because the cholesterol lowering drug, simvastatin, has been reported to attenuate inflammation by inhibiting the TLR4 pathway [8], the current study was designed to determine whether neonatal ERT, alone or in combination with oral simvastatin (ERT+S) could attenuate intervertebral disc disease in the canine model of MPS I.

Methods: Animal studies were performed following IACUC approval. Four age-matched groups were studied (each n=5): normal controls, MPS I untreated, MPS I ERT treated, and MPS I ERT+S treated. MPS I dogs were identified at birth by DNA mutation analysis. Treatments commenced at 1 week-of-age, and all animals were euthanized at 12-months-of-age. ERT consisted of weekly, 2-hour intravenous infusions of 0.58 mg/kg (the standard clinical dose for human patients). Simvastatin was administered orally once per week (2 mg/kg). Cervical spine MRIs were obtained immediately prior to euthanasia with intravenous 80mg/kg barbituate, and semi-quantitative grading schemes were used to evaluate disc condition (Pfirrmann grade) [9] and spinal cord compression [6] at each spine level (C2-C7). In addition, plain radiographs were obtained and disc height index (DHI) was determined. Single animal individual disc level data were averaged to determine a mean value for each spine. ANOVAs with post-hoc, pairwise Tukey’s tests were used to establish differences in each outcome measure between treatment groups (significant = p<0.05).

Results: Mean DHI for MPS I untreated and ERT alone were both significantly lower compared to normal (p<0.05), while ERT+S was not significantly different (Fig 1A). Mean Pfirrmann grade was significantly greater for MPS I untreated compared to normal, while for ERT and ERT+S, Pfirrmann grade was not significantly different from any other group (Fig 1B). Mean spinal cord compression severity was significantly greater for MPS I untreated compared to normal, while for both ERT, and ERT+S it was not significantly different from any other group (Fig 1C). For both Pfirrmann grade and spinal cord compression severity, ERT+S was modestly, but not significantly, improved relative to ERT alone. Representative MRI images from each group are shown in Figure 2.

Discussion: These results suggest that ERT commenced from a very early age attenuates some components of cervical spine intervertebral disc disease in MPS I, in agreement with previous findings [6]. The importance and potential benefits of delivering ERT as early as possible are supported by recent clinical findings [10]. There is evidence that simvastatin has anti-inflammatory properties that may be beneficial to reducing inflammation associated protease activity in the disc. As inflammation and associated destructive proteases are considered to play a significant role in the progression of disc disease in MPS I, we evaluated whether supplementation of ERT with simvastatin would lead to a further reduction in disc disease. Our findings here suggest that supplementation with simvastatin provided a small additional benefit over ERT alone.

Significance: MPS I is associated with debilitating spine disease. This study evaluates novel therapeutic strategies for attenuating spine disease in MPS I, which have the potential to improve patient longevity and quality of life.

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Figure 1: Effects of ERT and ERT+S (simvastatin) on A. Disc Height Index (DHI). B. Disc Pfirrmann grade. C. Spinal cord compression severity. *p<0.05 vs Normal.

Figure 2. Representative MRI images for each group showing examples of spinal cord compression (*) and disc degeneration (arrows).