High Dose Enzyme Replacement Therapy Attenuates Joint Disease Progression and Preserves Mobility in Mucopolysaccharidosis VII Dogs

Rahul Gawri
Yian Khai Lau
George R. Dodge
Carla R. Scanzello
Stephanie Jo
Chenghao Zhang
Wilfried Mai
Margret L. Casal
Lachlan J. Smith

University of Pennsylvania
Philadelphia, PA

Introduction

Mucopolysaccharidosis VII (MPS VII) is a lysosomal storage disorder characterized by impaired activity of the enzyme β-glucuronidase (GUSB), leading to aberrant accumulation of incompletely degraded chondroitin, dermatan and heparan sulfate glycosaminoglycans (GAGs).[1,2] Synovial joint disease is common in MPS VII patients, and manifests as joint stiffness and limited range of motion, thought to result from abnormalities in the ligaments, joint capsules, and underlying epiphyseal bone.[1,2] Intravenous enzyme replacement therapy (ERT) for MPS VII using recombinant human GUSB (rhGUS, Mepsevii®) has shown promising results in clinical trials.[3,4] While previous studies have evaluated rhGUS ERT in MPS VII mice,[5] there have been no such evaluations in large animal models of MPS VII. The naturally occurring canine model of MPS VII presents advantages over mouse models, including more closely recapitulating the nature and progression of skeletal disease manifestations that occur in human patients. The objective of this study was to investigate the effects of intravenous ERT using Mepsevii®, administered at two dose levels: the standard clinical dose (4 mg/kg, SD) and a high dose (20mg/kg, HD), on synovial joint disease progression in MPS VII dogs.

Methods

With IACUC approval, MPS VII affected dogs were treated from birth with intravenous Mepsevii® at either the standard clinical dose (ERT SD, 4mg/kg, n = 5) or a high dose (ERT HD, 20mg/kg, n = 3). Bolus administrations were given at 2 and 9 days-of-age, the first 2-hour infusion performed at 23 days-of-age, and subsequent 2-hour infusions were every 14 days. For ERT HD animals, prophylactic dexamethasone was required to prevent adverse reactions (nausea, vomiting and rash). Control animals included MPS VII affected untreated dogs (n = 6) and untreated heterozygous controls (n = 6). An additional control group of MPS VII dogs (n = 3) received dexamethasone without ERT. Monthly physical examinations were performed to assess ability to ambulate and joint swelling. All animals were euthanized at 6 months-of-age. Synovial fluid was collected for measurement of inflammatory biomarkers using a multiplex enzyme immunoassay. Synovial membrane and articular cartilage were harvested for assessment of enzyme (GUSB and hexosaminidase (HEX)) and GAG content. Excised stifle joints were imaged using 3T MRI, and pathological changes in major joint tissues, including cartilage, synovial fluid, meniscus, fat pad and subchondral bone assessed using a custom grading scheme.

Results

All MPS VII untreated animals exhibited a profound decline in mobility over the study duration. By 6 months-of-age, these animals were no longer ambulatory, and had severe joint effusions in all limbs and marked loss of muscle mass. MPS VII ERT SD animals exhibited somewhat attenuated progression of joint disease and decline in mobility, but by 6 months-of-age, all were no longer ambulatory, and all but one exhibited joint effusions similar to untreated. In contrast, MPS VII ERT HD animals exhibited more marked attenuation of joint disease and less decline in mobility. By 6 months-of-age, all three animals were still ambulatory, bright, alert and responsive. MPS VII steroid control animals were no longer ambulatory by 6 months-of-age and clinically indistinguishable from untreated. MPS VII dogs treated with Mepsevii® exhibited elevated rhGUS activity, and corresponding lower HEX activity and GAG content in synovial membrane (Figure 1). Results were dose-dependent, with ERT HD animals exhibiting higher rhGUS, and lower HEX and GAG compared to ERT SD animals. ERT HD animals exhibited significant attenuation of joint pathology assessed by MR imaging in the synovium, patella, meniscus, and fat pad (Figure 2) and reduced expression of inflammatory biomarkers in synovial fluid (Figure 3). Clinical and imaging findings (Figure 2A) from animals administered steroid alone suggests improvements in joint disease are attributable to ERT and not the steroid.

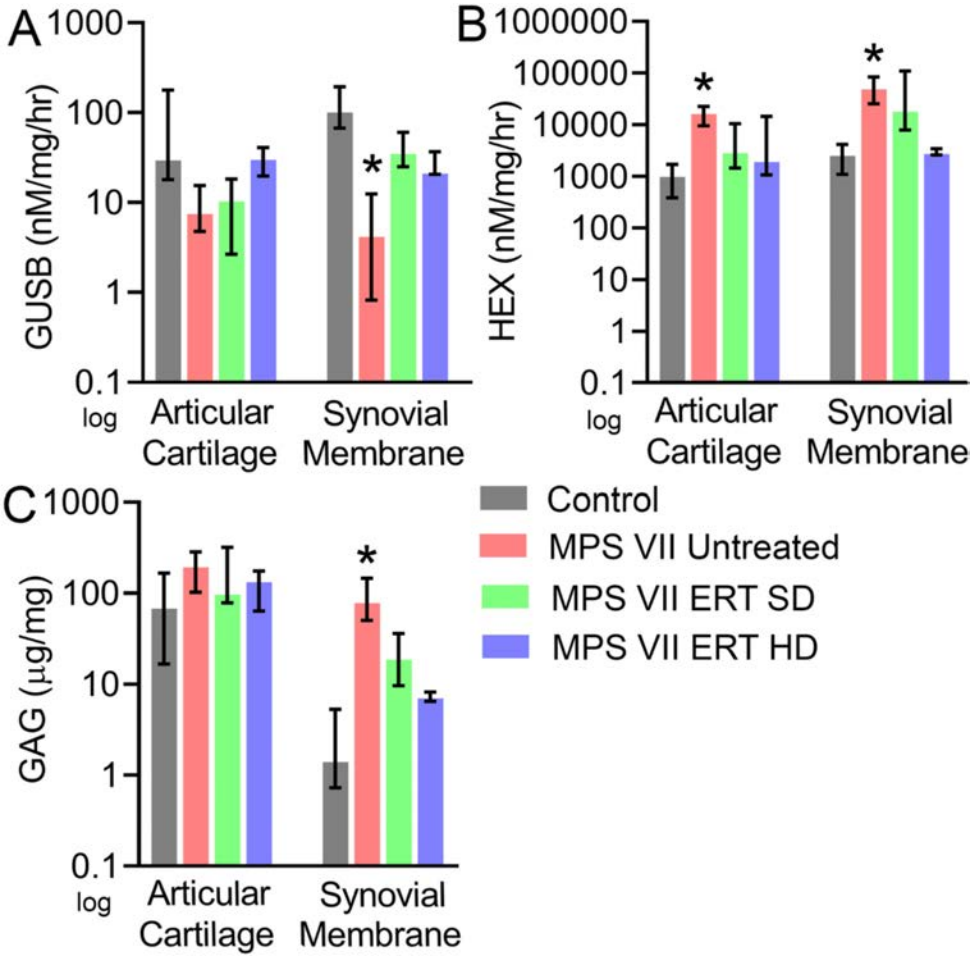

Figure 1. (A) GUSB. **(B)** HEX and **(C)** GAG content in articular cartilage and synovial membrane. N=3-6; *p<0.05 vs Control.

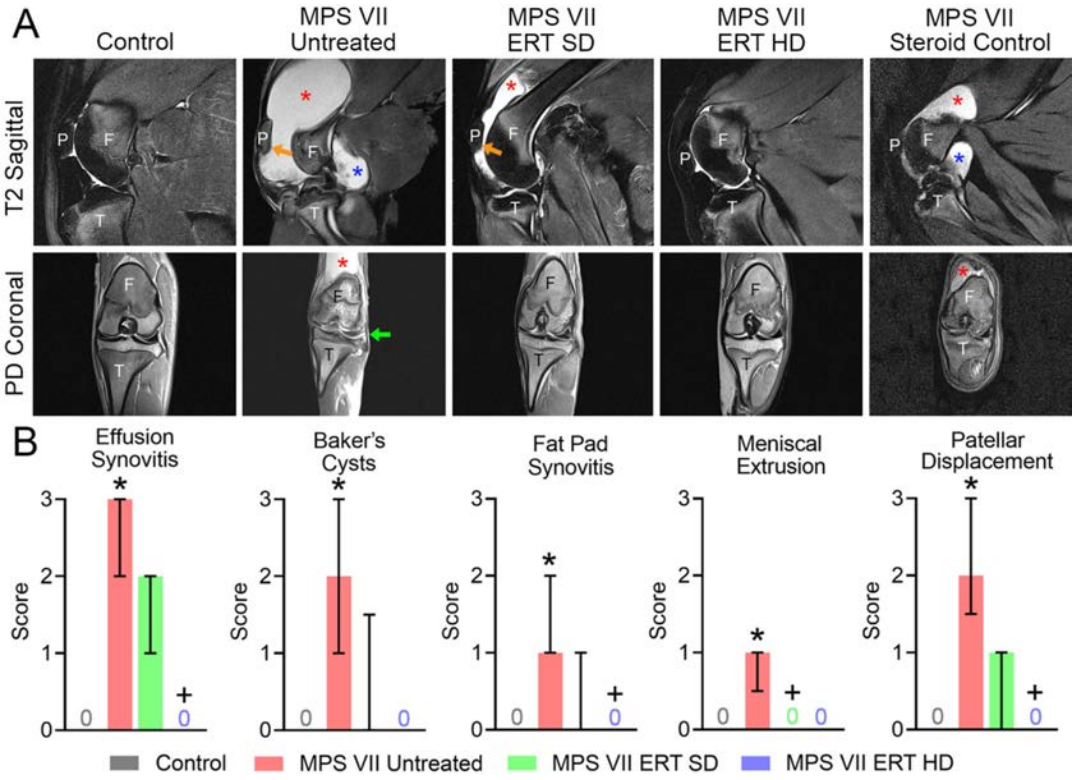

Figure 2. (A) MRI images of canine stifle joints showing synovial effusions (red *), Baker's cysts (blue *), patellar displacement (orange arrows) and meniscal extrusion (green arrow). **(B)** Semi-quantitative grading of pathological features. N=3-6; *p<0.05 vs Control; +p<0.05 vs Untreated MPS VII.

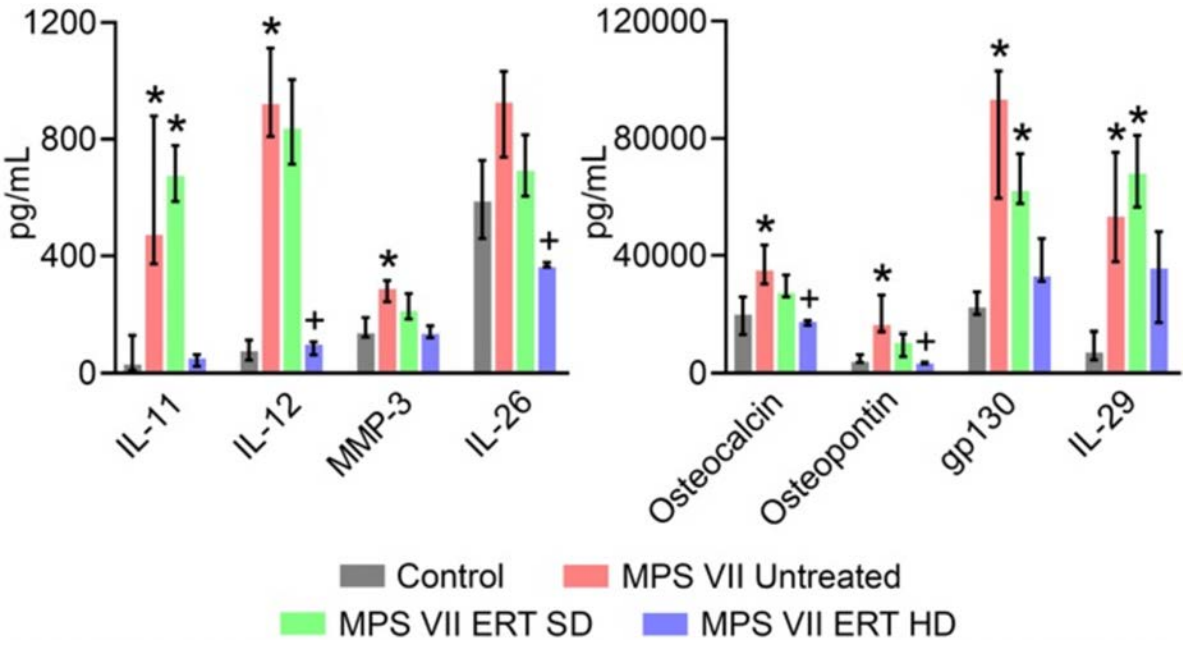

Figure 3. Inflammatory biomarker expression in stifle joint synovial fluid. N=3-6. *p<0.05 vs Control; +p<0.05 vs Untreated MPS VII.

Conclusions

Overall, our findings indicate that Mepsevii® administered shortly after birth at the higher dose of 20mg/kg compared to the standard clinical dose of 4mg/kg results in improved clinical outcomes with respect to joint pathology and mobility in MPS VII dogs. Should these findings be replicated in the clinic, attenuation of synovial joint disease and preservation of mobility has the potential to significantly improve patient quality of life.

Significance

MPS VII patients exhibit severe synovial joint disease resulting in chronic pain and impaired mobility, negatively impacting quality of life. Here we demonstrate that high dose ERT results in a significant improvement in joint disease and mobility in a clinically relevant large animal model.

Acknowledgments

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References

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