Pharmacology of Small Molecule Inhibitors of GYS1 in Canines and a Mouse Model of Pompe Disease

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Introduction

Pompe disease is a glycogen storage disease caused by mutations in the enzyme acid alpha-glucosidase, resulting in pathological accumulation of glycogen. Glycogen can accumulate in virtually all tissues, but the primary pathology affects skeletal and cardiac muscle. Current standard of care treatment for Pompe patients consists of enzyme replacement therapy (ERT) with human recombinant GAA (Byrne et al., 2011). ERT treatment has been life saving for infant-onset Pompe disease (iPOMO) patients, and significantly slows the rate of disease progression in late-onset Pompe Disease (LOPD) patients. However, for both patient populations the beneficial effects of ERT generally plateau within a few years of treatment, after which the disease continues to progress; an unmet need remains for an effective and safe treatment for Pompe disease (Schoen, 2019, Meena et al., 2020).

Glycogen is the rate-limiting enzyme in muscle glycogen biosynthesis. In mouse models of Pompe disease, reducing glycogen synthesis via genetic ablation of GYS1 attenuates glycogen accumulation and muscle pathology (Douillard-Guilloux et al., 2010). MEZ001 and MZ-101 are novel, selective, small molecule inhibitors of muscle glycogen synthase 1 (GYS1) under development at Masa Therapeutics. We propose that by inhibiting glycogen synthesis, tissue glycogen content and its associated toxicity will be reduced in Pompe patients. Figure 1 illustrates our therapeutic hypothesis.

**Figure 1. Schematic of restoration of glycogen homeostasis in Pompe cells after Substrate Reduction Therapy (SRT)**

**Figure 2. Schematic of acute, de novo glycogen synthesis study design**

**Figure 3. MZE001 and MZ-101 potently inhibit glycogen synthesis in skeletal muscle but not liver in Pompe Mice**

Male Pompe mice were dosed as indicated in Figure 2. MZE001 and MZ-101 potently inhibit glycogen synthesis in Pompe gastrocnemius and diaphragm in a dose-dependent manner, indicating on-target GYS1 inhibition in vivo. Glycogen synthesis in the liver is not altered by MZE001 or MZ-101.

**Figure 4. SRT/ERT combination reduces glycogen & cellular dysfunction**

SRT/ERT combination normalizes glycogen and cellular dysfunction (LAMP1, LAMP2, GADPH) in heart and gastrocnemius tissues from Pompe mice, whereas ERT alone does not normalize glycogen levels. Values plotted as mean ± SEM.

Conclusions

1. MZE001 and MZ-101 potently and specifically inhibit GYS1 in vivo.
2. MZE001 reduces tissue glycogen, which strongly correlates with decreased biomarkers in dogs.
3. Chronic treatment with MZ-101 reduces elevated glycogen levels in Pompe mouse skeletal muscle and is associated with improvements in markers of cellular dysfunction.
4. Combination therapy of MZ-101 + ERT normalizes tissue glycogen and restores cellular homeostasis.

References & Acknowledgments


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