Inhibition of Glyoxalate Oxidase (HAO1) with Dicer-Substrate siRNAs as a Substrate Reduction Therapy for Primary Hyperoxaluria Type I

Abstract

Primary Hyperoxaluria type 1 (PH1) is an autosomal recessive disorder involving the overproduction of oxalate. Oxalate is an end product of metabolism that is mainly produced in the liver and excreted by the kidney. High concentration of urinary oxalate and the subsequent formation of highly insoluble calcium oxalate, resulting in urolithiasis, nephrocalcinosis, chronic kidney disease and ultimately renal failure in PH1 patients. Currently, treatment options for this devastating and primarily pediatric disease are very limited. PH1 is caused by an enzyme deficiency of alanine-glyoxylate aminotransferase (AGT), the human peroxisomal enzyme that converts glyoxylate to glycine. One potential therapeutic approach for PH1 would be to inhibit glyoxalate oxidase (GO), thereby reducing the amount of glyoxylate produced and oxalate formation. GO has been previously established as a safe and effective target for PH1 through substrate reduction using an AGT-deficient PH1 mouse model with additional knockout of GO. In this study, dicer-substrate siRNAs (DsiRNAs) were designed and delivered by proprietary lipid nanoparticle (LNP) formulation to efficiently knockdown GO (HAO1) expression in liver. The leading HAO1 DsiRNA durably abolished GO mRNA and protein production while also significantly reducing oxalate excretion in hyperoxaluric AGT-deficient mice. Long-term treatment with an efficacious dose of HAO1 DsiRNA was well tolerated suggesting an achievable therapeutic window for the use of DsiRNA therapeutics for PH1 and potentially other liver diseases. In conclusion, inhibition of GO activity through administration of HAO1 DsiRNA reduces the hyperoxaluric phenotype in the AGT-deficient mouse model of PH1 and warrants further clinical investigation.

HAO1 KD Leads to Oxalate Reduction in PH1 Mice

Oxalate Metabolism and Potential Targets for PH1

HAO1 DsiRNA/LNP Displays Long-Term Tolerability

Improved Modified Immunosilent DsiRNA Retains High Activity

Summary

- HAO1 is a safe and effective target for Primary Hyperoxaluria Type I
- DsiRNAs delivered by an LNP formulation efficiently abolish GO mRNA and protein production, resulting in oxalate reduction in hyperoxaluric AGT-deficient mice.
- Urinary glyoxylate is a potential additional PD biomarker
- HAO1 DsiRNA with improved modifications reduces immunostimulatory activity
- Long-term treatment with an efficacious dose of HAO1 DsiRNA is well tolerated in mice
- HAO1 DsiRNA approach warrants future clinical investigation