Epalrestat monotherapy in a Single Patient with Phosphomannomutase 2 Deficiency (PMM2-CDG)

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Background & Objectives

- Effective treatment for PMM2-CDG remains an unmet need. A potential path to therapy for PMM2-CDG is small-molecule drug repurposing.
- In our previous study, we showed that epalrestat was able to increase PMM2 enzyme activity in multiple PMM2-CDG patients' fibroblasts in vitro[1].
- We used the oral aldose reductase inhibitor (ARI) epalrestat in a 6-year-old girl with PMM2-CDG.
- Here, we report on the first single-patient observational safety and efficacy study of epalrestat treatment in a PMM2-CDG patient, and the implication of epalrestat as a novel therapeutic for PMM2-CDG.

Patient Outcomes

Figure 1

Transferrin Glycoform ratios vs. growth

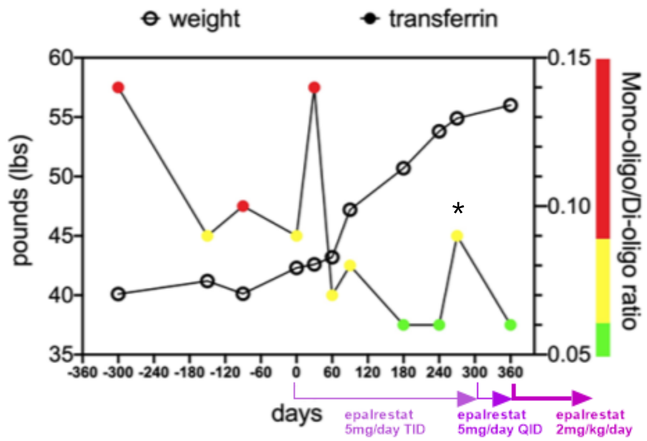


Figure 2

Epalrestat PK Profile

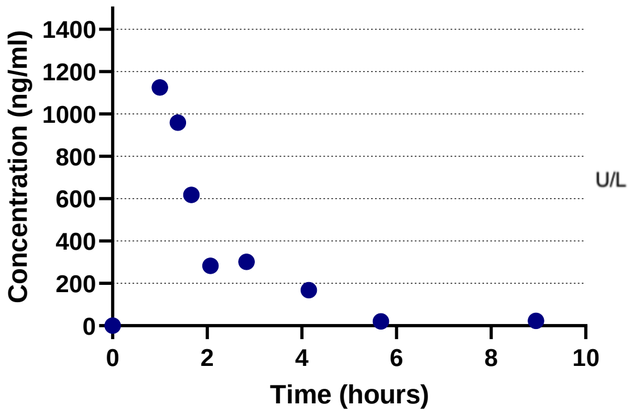
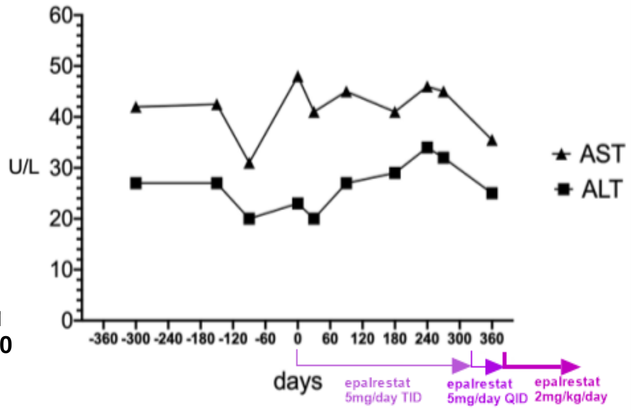


Figure 3

Liver transaminases



Methods

- We prospectively followed a single patient on epalrestat treatment for 12 months.
- Epalrestat was administered 3 times per day, orally at a dose of 0.8 mg/kg/day.
- As a part of the safety assessments, we monitored serum epalrestat levels and liver health by laboratory follow-up testing and imaging over the course of the study.
- To evaluate the efficacy of epalrestat we measured Transferrin Glycoform ratios and monitored, growth (BMI), ataxia (ICARS) and clinical disease progression using the Nijmegen Pediatric CDG Rating Scale (NPCRS).

Safety and efficacy measurements

- Increasing BMI during epalrestat therapy and blood transferrin glycoform ratio analysis by mass spectrometry 12 months prior to therapy and during 12 months of epalrestat therapy (**Figure 1**). Normal level <=0.06. *Patient has been underdosed due to unexpected weight gain, with dose correction to 0.8mg/kg/day at 11 months.
- The pharmacokinetics profile shows rapid elimination of epalrestat. Each epalrestat blood concentration measurement was performed after dosing on a different day because of limitations on the number of daily blood draws. Epalrestat was eliminated with a t½ of ~1-2 hours. (**Figure 2**)
- Normal liver transaminases levels across the study period (ALT Ref. Range: 7-45 U/L; AST Ref Range: 8-50 U/L) (**Figure 3**). Liver elastography showed Liver Stiffness Values prior to treatment equal to 5.7 kPa and at 9 months it was 5.3 kPa (reference for a nonfibrotic liver is 0.0-7.2 kPa).
- The NPCRS indicated a minimal improvement from a baseline of 21-24 in the 6-month period before the trial to a score of 20-21 in months 6-12.
- ICARS ataxia score improved from 56 to 42.

Discussion

- Epalrestat has been recently demonstrated to have a positive effect in the treatment of PMM2-CDG by up-regulating PMM2 enzyme activity *in vitro*.
- Epalrestat blocks aldose reductase activity and alters the flux in the polyol pathway away from sorbitol production, thereby making more glucose available for the production of glucose 1,6 bisposphate. This metabolite is a known activator of PMM2 enzyme activity.
- Notably, epalrestat had a positive effect on the glycosylation defect during the 12 months of therapy, in particular months 6-12.

Conclusions

- There is an urgency in finding novel treatments for CDG.
- Epalrestat could be a novel repurposed drug for the treatment of PMM2-CDG.

Reference

1. Iyer, S., Sam, F. S., DiPrimio, N., Preston, G., Verheijen, J., Murthy, K., Parton Z., Tsang H., Lao J., Morava E., Perlstein, E. O. (2019). Repurposing the aldose reductase inhibitor and diabetic neuropathy drug epalrestat for the congenital disorder of glycosylation PMM2-CDG. Disease Models & Mechanisms, 12(11), 11.\