Background

Glycogen storage disease Ib (GSD Ib) is an autosomal recessive condition caused by variants in SLC37A4, which encodes for glucose-6-phosphate translocase (G6PT). G6PT transports cytoplasmic glucose-6-phosphate to the endoplasmic reticulum where it is oxidised by the enzyme, glucose-6-phosphatase, to release free glucose. GSD Ib is characterised by hepatomegaly, severe hypoglycaemia and failure to thrive.

A hallmark feature of GSD Ib is neutropaenia and neutrophil dysfunction. Recent evidence has demonstrated this to be the result of accumulated 1,5-anhydroglucitol-6-phosphate (1,5AG6P) in neutrophils; impairing neutrophil glycolysis.1

Subcutaneous granulocyte colony-stimulating factor (G-CSF) has traditionally been the mainstay of treatment however, the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors is becoming more widespread to treat neutropaenia and neutrophil dysfunction.2

SGLT2 inhibitors, such as Empagliflozin, functions to increase urinary glucose excretion and in doing so reduces renal re-absorption of 1,5-anhydroglucitol (1,5-AG); lowering its serum concentration. Here we report the use of a SGLT2 inhibitor in a GSD Ib patient who has undergone liver transplantation (LT).

Case report

The patient was diagnosed with GSD Ib in the neonatal period; presenting with recurrent hypoglycaemia and hyperlactataemia. Molecular testing demonstrated bi-allelic SLC37A4 variants.

Despite medical management the patient had poor metabolic control; impacting on quality of life, and underwent split LT at 19 months of age. Post LT complications have included mild-moderate acute cellular rejection, biliary outflow tract obstruction and protracted post-infectious colitis. The patient suffered from recurrent oral ulcers and infective illnesses post LT, including poor wound healing following gastrostomy removal.

He remained on G-CSF therapy three days weekly (6mcg/kg/dose) with an absolute neutrophil count (ANC) consistently <1.5x10^9/L, including as low as 0.2x10^9/L, outside of infective illnesses. Empagliflozin, at a dose of 2.5mg once daily (0.2mg/kg/day) was commenced during an inpatient admission with foot cellulitis at age 3.5 years.

Results

Following commencement of Empagliflozin the patient had morning blood glucose levels (BGL) ranging between 2.2 – 3.4 mmol/L, including a single symptomatic episode (BGL 1.8mmol/L). Introduction of a pre-bedtime small meal has improved this.

On clinical review one month following Empagliflozin commencement the patient has had improvements in his oral health in addition to, reduced leakage from his previous gastrostomy site.

The patient’s neutrophil count upon starting Empagliflozin improved and allowed complete weaning of G-CSF therapy after four weeks (see Figure 1). Measurement of plasma 1,5-anhydroglucitol (1,5AG) utilising the GlycoMark® assay demonstrated a reduction in plasma levels (60 uM → 38.9 uM) within a month of treatment commencement (see Figure 2).

Discussion

Demonstrated clinical benefits of Empagliflozin in patients with GSD Ib include, improved neutropaenia and neutrophil dysfunction, and a reduction in the burden of gastrointestinal symptoms.2,4 Benefits in our patient post LT to date has included improvements in wound healing, oral health and ANC. Measurement of plasma 1,5AG in our patient has been valuable in demonstrating treatment response.

The introduction of Empagliflozin has allowed for cessation of G-CSF therapy, which is not only painful in its route of administration but long-term use has been associated with an increased risk of malignancies and splenomegaly. Furthermore, the cost of Empagliflozin therapy is significantly less than G-CSF therapy.

Our experience has demonstrated that the risk of hypoglycaemia secondary to glycosuria with Empagliflozin therapy is present despite LT. We therefore recommend a low-dose at initiation of therapy and careful up-titration with monitoring of BGL to prevent hypoglycaemia.

References