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SGLT2i safely and completely restores immune competence in adults with GSD1b: A case report

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Abstract

The role of intracellular accumulation of 1,5-anhydroglucitol 6-phosphate (1,5AG6P) in the pathogenesis of neutropenia in glycogen storage disease type ib (GSD Ib) has recently been demonstrated. Patients with GSD Ib show severe hypoglycemia after short fasting (approximately 2-4 hours), hepatomegaly, hyperlactatemia, hyperlipidemia, hyperuricemia, failure to thrive, neutropenia/neutrophil dysfunction, and increased risk of inflammatory bowel disease and autoimmune diseases. The demonstration of the role of intracellular accumulation of 1,5AG6P in the pathogenesis of neutropenia/neutrophil dysfunction has recently formed the basis for the development of new therapeutic strategies for Ib GSD. These are oral hypoglycemic drugs approved for the treatment of type 2 diabetes which inhibit the renal reabsorption of both glucose and 1,5AG. The aim of this report is to describe the clinical experience in the maximal use of empagliflozin, in a hospital and home setting, in an adult patient with GSD 1b and severe neutropenia complicated by Inflammatory Bowel Disease. Patient response to the therapy was excellent without recorded adverse effects. This was probably because the pharmacological therapy was accompanied by a balanced nutritional plan that allowed blood sugar levels to be maintained as close to normal as possible.

Keywords: GSD1b (glycogen storage disease type ib); 1,5AG6P (1,5-anhydroglucitol 6- phosphate); Liver glycogen storage diseases; Rare diseases; Research; Balanced nutritional plan; Neutropenia/neutrophil dysfunction; sglt-2 inhibitor; Inflammatory bowel disease; Neutropenia; Empagliflozin.

Introduction

Glycogen storage disease type Ib (GSD Ib, MIM#232220) [1] is an autosomal recessive inherited disorder of carbohydrate metabolism (prevalence about 1/500,000) caused by mutations in the SLC37A4 gene encoding the microsomal glucose 6-phosphate transporter (G6PT), ubiquitously expressed [2,3]. Patients with GSD Ib show severe hypoglycemia shortly after fasting (approximately 2-4 hours), hepatomegaly, hyperlactatemia, hyperlipidemia, hyperuricemia, failure to thrive, neutropenia/neutrophil dysfunction, and increased risk of inflammatory bowel disease and autoimmune diseases [4].

Diet is effective to help controlling the metabolic features of the disease and preventing clinical symptoms of hypoglycemia. It often involves the use of continuous or nocturnal enteral nutrition, and the regular intake of slow-absorption cornstarch. Dietary therapy provides sufficient glucose for the body's meta-

bolic needs, preventing episodes of severe hypoglycemia as well as limiting glycogen accumulation in liver and kidney, and the resulting metabolic alterations responsible for the typical GSD1 metabolic symptomatology [5].

Yet, despite controlling the metabolic symptoms, regular cornstarch intake does not improve the immunological manifestations (also present in GSD Ib patients), which also have a strong impact on patients' prognosis and quality of life. Neutropenia and neutrophil dysfunction (present in more than 80% of patients with GSD Ib) results in frequent hospitalizations due to severe (sometimes life-threatening) infections and the development of inflammatory bowel disease [6]. The origin of the pathophysiological mechanism affecting the neutrophils remained unclear for a long time, making it difficult to design specific and effective therapies. To date, granulocyte colony-stimulating factor (G-CSF) is the only approved treatment option for alleviating neutropenia in patients with GSD Ib, despite being burdened with long-term side effects [7,8].

Recently Veiga-da-Cunha and collaborators have shown that it is the intracellular accumulation of 1,5-anhydroglucitol 6-phosphate (1,5AG6P) in neutrophils of GSD Ib patients that is responsible for the pathogenesis of neutropenia. 1,5-AG6P, results from the phosphorylation of 1,5-anhydroglucitol (1,5-AG), which is present in food and is the most abundant polyol in blood [9]. Consequently, it was found that G6PT has two physiologically important functions: (1) in liver and kidney cells, G6PT transports glucose-6-phosphate into the lumen of the endoplasmic reticulum (ER) where it is dephosphorylated by glucose-6- phosphatase (G6PC1) to form glucose, preventing hypoglycemia during the fasting periods; (2) In neutrophils and other white blood cells, G6PT transports 1,5-AG6P into the ER where it is dephosphorylated by G6PC3, a ubiquitously expressed phosphatase that does not dephosphorylate glucose-6-phosphate but prevents 1,5-AG6P from accumulating in cells [10]. 1,5-AG6P is a potent inhibitor of hexokinases and therefore of glycolysis, explaining the origin of neutropenia and neutrophil dysfunction in GSD1b and G6PC3-deficient patients [10,11].

This discovery has recently formed the basis for the development of new therapeutic strategies for neutropenia in GSD Ib. To this end, since 1,5AG is present in most foods and predominantly of dietary origin, pharmacological treatments that increase the urinary excretion of 1,5-AG have therefore been explored. In this context, gliflozins that are molecules that inhibit SGLT2, the main Na^+-glucose cotransporter in the kidney that is present in the proximal tubule have been explored. These SGLT2-inhibitors (SGLT2i), such as empagliflozin, canagliflozin or dapagliflozin, are oral glucose-lowering drugs approved for the treatment of type 2 diabetes. When used, SGLT2i, prevents the renal reabsorption of glucose and increases its concentration in the renal filtrate. This indirectly prevents 1,5-AG reabsorption, which is also filtered in the kidney and present in the renal filtrate, by its own transporter, SGLT5 [12]. Under normal conditions, in the absence of SGLT2i, SGLT5 reabsorbs 1,5-AG, but also mannose and fructose but not glucose from the urinary filtrate. Yet, in the presence of i-SGLT2i, the increase in the concentration of glucose, competes with the reabsorption of 1,5AG by SGLT5 and promotes its urinary excretion together with the observed glucosuria. It is by this mechanism that SGLT2i indirectly lowers the level of 1,5- AG in blood and 1,5-AG6P in neutrophils [10,13].

Lowering 1,5-AG6P decreases its inhibition on hexokinases, which increases the availability of glucose-6-phosphate for glycolysis, the pentose phosphate pathway and protein glycosylation, all shown to be impaired in neutrophils from GSD Ib and G6PC3-deficient patients [14,15]. Among the SGLT2i that have been repurposed to treat neutropenia in GSD Ib patients, empagliflozin is the most widely used [16,17]. Yet, clinical experience in adults is still limited and a method for reducing the risk of hypoglycemia in these patients during SGLT2i therapy has not yet been standardized.

The purpose of this report is to describe the clinical experience of empagliflozin at full dosage, in a hospital and home setting, in an adult patient with GSD Ib and severe neutropenia complicated by severe IBD.

Material and methods

Patient description

A 27 years old female, weight 62 Kg and body mass index 23 Kg/m2, was diagnosed with GSD Ib at the age of 5 months due to the presence of frequent episodes of hypoglycemia associated with a deficiency in the microsomal transport of glucose-6-phosphate on a liver biopsy and genetic testing (G6PT53 mutation). The defect in G6PT was genetically confirmed following the molecular investigation of the G6PT gene on DNA isolated from peripheral blood lymphocytes. All exons of the SLC37A4 gene (coding for G6PT) were analyzed by Single-Strand Conformation Polymorphism (SSCP) and the exons that were shifted were sequenced showing that the patient is a compound heterozygous for a mutations in exon 1 (252G->A; pArg28Cys) also found in the maternal sample, and in exon 4 (911C->T; pGln-248Stop) also found in the paternal sample (G6PT53 mutation: SLC37A4 gene, coding for G6PT) [18].

Since the age of 6 years she has been on cyclic therapy with G-CSF for severe neutropenia, but remained neutropenic and developed hepatic adenomas, orogenital mucosal lesions, and frequent infectious episodes.

After hospitalization due to abdominal recurrent pain, endoscopies with biopsies showed esophagitis with minimal lesions, and non-specific pattern of chronic ileocolitis then complicated with anemia with microcholelithiasis and multiple vitamin deficiencies due to intestinal malabsorption. Liver and spleen were enlarged (longitudinal diameter of liver left lobe 16 cm, max normal 14 cm; 13 cm spleen length max normal 12 cm [19]). Furthermore, she had severe daily hypoglycemia episodes despite a cornstarch diet with nocturnal nasogastric tube feeding.

Before starting treatment with empagliflozin the patient was taking the following medication: ursodeoxycholic acid 300 mg, 1 tablet bis in die; mesalamine 800 mg, 1 tablet ter in die; budesonide 3 mg, 1 tablet ter in die; vitamin supplements; G-CSF 30 UI every 5 days.

Experimental protocol

Study design included a 10 days hospital admission as an inpatient with 4 evaluation day points, and a follow-up at home during the next 6 months with outpatient visits approximately

every 6 weeks. During each visit, a full clinical evaluation was performed: abdominal circumference, body weight, Bristol Stool Scale (BSS, classifying feces shapes into seven categories, from 1 (difficult to evacuate) to 7 (diarrhea), where normal values are central ones [20]), Crohn's Disease Activity Score (CDAI, a scoring system where normal value is below 150 [21]), fecal calprotectin (normal value under 50 mg of calprotectin/kg of stool [22]), blood cell count, C-Reactive Protein (CRP), measurement of the concentration of 1,5-AG in plasma (normal range 12-29 micromolar [23]) and 1,5-AG6P in isolated white blood cells.

Blood glucose during the first 10 days of treatment were measured by continuous glucose monitoring and additional capillary measurements every two hours. Flash Glucose Monitoring (FGM) was carried out with a non-invasive intelligent device/sensor whose system involves the use of a subcutaneous sensor on the back of the arm, which allows to check subcutaneous glucose levels at any time of the day simply by bringing the reader (which can also be a mobile phone) to the sensor (Freestyle Libre 2 - Abbott Laboratories Limited - Rome (IT)). The system sends alarms, alerts and notifications related to glucose values visible at any time on the smartphone app. The patient can therefore see the curve and trends of his actual subcutaneous glucose levels and is warned through sounds and vibrations before reaching too high or too low values. FGM also indicates the Time Below the Range (TBR), i.e. the percentage of time during which the glycaemia measured by the sensor is lower than the defined target (70 mg/dL). As a reference, blood glucose measurements using FGM were compared with those using commercially available glucometers, on a blood drop taken from a fingertip to measure directly the concentration of glucose at specific times.

Glucosuria was monitored daily during empagliflozin treatment and the intake of cornstarch was increased in accordance with the amount of glucose lost in urine.

Off-label therapy was approved by the local ethics committee of the Mater Domini Hospital of the Magna Græcia University of Catanzaro. After signing a written informed consent in January 2022, the patient was admitted to the Metabolic Diseases Unit of the hospital.

Empagliflozin was given in the morning in a single daily dose irrespective of cornstarch assumption and incrementally increased until it reached 25 mg that is the maximum adult daily dose). The first dose of empagliflozin (10 mg) was given 48 hours after the last dose of G-CSF and increased on the third day to 2 x 10 mg given in the morning and in the evening. This lasted until day 44 after which empagliflozin was further increased to 25 mg given in a single daily dose for the remaining period of treatment that is reported.

When in hospital, the patient followed an ad hoc personalized food plan which was maintained once she had gone home. In order to keep the level of glucose in blood stable, it was recommended to eat every 3 hours (3 main meals and 5 snacks), even during the night, mainly foods slowly and gradually releasing glucose as below reported. The caloric breakdown was 70% carbohydrates, 15% fats, and 15% proteins. It was recommended to avoid milk and mature cheeses, overcooked pasta and rice, white bread, boiled potatoes, rusks and breadsticks, and in general sucrose-rich foods including some vegetables and fruits. The diet also included olive and soy oil that were taken together with cornstarch ("Maizena" - Unilever PLC, London-UK) to slow down its digestion and allow for an optimal absorption of the glucose in the bowel and its slower release into the circulation, which helped to increase the time between meals, especially at night [24].

Quantification of 1,5-AG in plasma 1,5-AG6P in neutrophils

1,5-AG (in plasma) and 1,5-AG6P (in neutrophils) were both quantified by Liquid Chromatography - Mass Spectrometry (LCMS) as previously described [25,26]. Practically, 1,5-AG in plasma was extracted by adding 2 µl of plasma 45.5 µl of a solution containing 81% methanol, 10% H2O and 9% chloroform and 2.5 µl of deuterated 30 µM 2-[D]-1,5AG (m/z = 164.0674), which was used as an internal standard to allow estimation of plasma 1,5- AG (m/z = 163.0612). Absolute concentrations were determined by comparing the integrated extracted ion chromatograms corresponding to 1,5-AG with those of the internal standard [10]. For 1,5-AG6P it was determined during treatment by Liquid-Chromatography-Mass Spectrometry (LC-MS) in blood cells after plasma removal (for 1,5-AG determination) and normalized to total metabolite content (total ion current, TIC) and Absolute Neutrophil Counts (ANC) [10].

Results

Hospital admission period

Empagliflozin treatment was started in hospital with a 10 mg tablet given in the morning after breakfast. After 3 days, when the dose reached was increased to 2 x 10 mg given in the morning and in the evening of treatment, the patient reported an increase in her appetite and ability to brush teeth without pain or bleeding. After 5 days, mouth and genital ulcers were healed. Within a week, stool frequency decreased from 2 to 1 per day, BSS score entered the normal range, stool calprotectin levels normalized as CDAI also decreased from 217 to below 100. The patient did not report any new bacterial infection. After 8 days, she referred general well-being: no fatigue, absence of abdominal pain, increased muscle strength.

Cornstarch taken by the patient was increased during therapy from 130 g/day (before starting empagliflozin) to 175 g/day during the therapy, based on the amount of glucose lost in urine. In this way, the blood glucose levels remained stable according to the values from continuous FGM measurements. Consequently, there were no symptomatic hypoglycemic episodes detected during treatment except for a few mild and asymptomatic ones (always above 65 mg/dL). The patient was discharged after 10 days and followed on an outpatient basis.

Outpatient management

While being treated at home, the patient continued to report a state of general well-being, she had increased energy, there were absence of lesions and infections of the oral and urogenital mucous membranes, absence of gastrointestinal disorders. This period of observation lasted for 4 months, after which a colonoscopy revealed normal results (complete absence of bowel mucosal lesions everywhere during the examination), whereas her abdominal ultrasound was unchanged as expected (hepatosplenomegaly need several years to recover, if any).

Budesonide and vitamin supplements were stopped after 2 weeks, and G-CSF injections were self-suspended after one month. After 45 days, empagliflozin was increased to its maximum dosage of 25 mg/day, with no side effects reported. Treatment with mesalamine was stopped after 3 months.

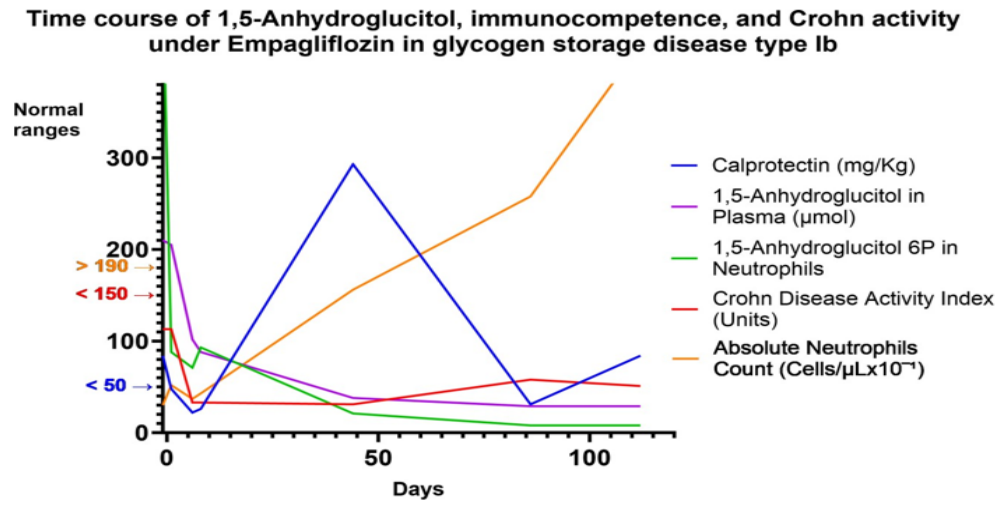

Figure 1: Compares variations of CDAI with calprotectin, together with the gradual increase in the absolute neutrophil count and the reductions of both plasma and neutrophils 1,5AG, until the normalization of all considered parameters.

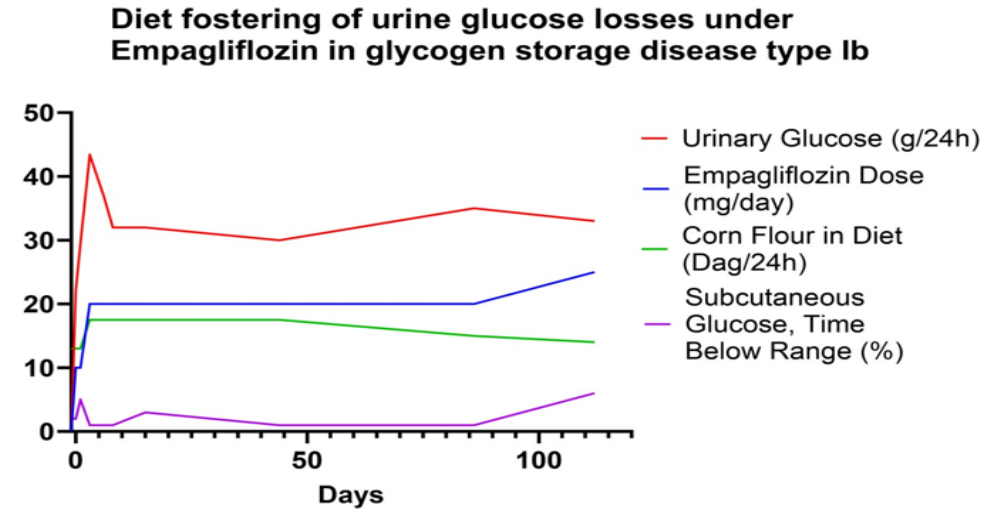

Figure 2: Illustrates the pharmacological increase of urinary glucose, balanced by the assumption of adequate doses of cornstarch in the diet, as demonstrated by the subcutaneous glucose monitoring in the day before visits. No severe hypoglycemia or loss of consciousness were reported throughout the study.

Daily FGM and the measurement of glycosuria were performed once in a week and ever in different weekly days, in order to take into account possible weekly and/or seasonal variations.

Discussion

Patient response to the empagliflozin 25 mg therapy (the maximal daily dose in adults, irrespective of body weight), in terms of blood cell count and consequently of infections, was excellent without adverse effects. Plasma and neutrophil 1,5AG6P promptly decreased, reaching approximately 10 times less in the 3 months of observation. Crohn's disease healed and the patient finally had a normal lifestyle without any other therapy or symptoms.

In literature, the few reported cases of SGLT2i in adults affected by GSD Ib demonstrated a lower therapeutic efficacy, as below reported.

The first report described a compound heterozygosity in a 21 years old female under empagliflozin 10 mg bis in die (adult daily dose ranges from 10 to 25 mg and it is prescribed irrespective of body mass or surface), clinically improved without side effects but yet neutropenic (500/microL). Plasma and neutrophil 1,5AG6P decreased 10 times, approaching normal values [25].

Briefly after, it was reported the case of a 35 years old female started from dramatic sequelae of bowel infections and their surgical excisions, who recovered until 2000/microL neutrophils (just above their minimum levels) with wide clinical benefit, after empagliflozin 20 mg/die. CDAI and clinical symptoms improved but without normalization. 1,5AG6P was not measured [27].

Then, it was reported the case of two adult brothers treated with empagliflozin 20 mg/die. For both, Bristol stool scale improved but without normalization and G-CSF was not stopped [28].

Furthermore, a 32 years old female was treated with empagliflozin 25 mg/die, obtaining almost a normalization of plasma 1,5AG6P, only a reduction of G-CSF administration and the resolution of bowel symptoms and therapy [23].

Finally, a wide retrospective questionnaire pool analysis was reported on 32 adults. The study design does not allow a full comparison with other literature data. However, among 25 pa-

tients with neutropenia, 36% reached normal cell values. In the whole group, therapy doubled patients with normal CDAI values, without reaching a full normalization in all individuals [16].

As a whole, therefore, the clinical response to the SGLT2i empagliflozin in literature is always impressive but generally lower than in the present case. Observation windows were similar for every clinical case. When reported, all patients had a compound heterozygosity, which was different among cases. Different empagliflozin dosages might influence clinical response, and surely an early starting along the disease history might reach better results. It is also possible that SLC37A4 gene polymorphisms, and/or SGLT2 - SGLT4 variants, might influence therapeutic response. The here reported young adult patient completely recovered in every aspect of immunosuppression manifestations, both clinical and instrumental (wherever possible) and laboratory features. She stopped every therapy for GSD Ib (apart from ursodeoxycholic acid for the preexistent microcholelithiasis), and for the first time he had a normal lifestyle.

Regarding expected side effects of the experimental therapy, the use of the glucose-lowering drug empagliflozin resulted in an increase in glycosuria which, however, stabilized over time. This is because the pharmacological therapy was accompanied by a balanced food plan that would allow us to maintain blood sugar levels as normal as possible, helping the patient with the calibration of the doses of cornstarch/day on glucosuria. By the monitoring of sugar via a subcutaneous device, it was possible to appreciate only some mild hypoglycemia, but never severe hypoglycemia. This effective minimally invasive approach (glycosuria and FGM measurements for 4 days in a month) might therefore represent a reference for monitoring systems in patients suffering from GSD Ib, allowing the patient to be confident about the compliance to the therapy and maximizing its beneficial effects.

Conclusions

GSD Ib is a rare disease known to cause hypoglycemia and to shorten life expectancy by immune deficiency. Controlled treatment with maximal doses of a hypoglycemic drug used in type 2 diabetes was shown here to be safe and effective in completely restoring the immune barrier of the patients, allowing such patients to normalize her quality of life. To further improve the treatment of this rare disease, maybe different choices within SGLT2i class, and the study of the genomic response to the therapy, might be important.

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