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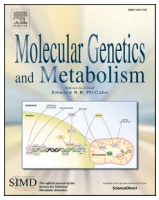

Review article

Treatment recommendations for glycogen storage disease type IB-associated neutropenia and neutrophil dysfunction with empagliflozin: Consensus from an international workshop

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ABSTRACT

Glycogen storage disease type Ib (GSD Ib, biallelic variants in *SLC37A4*) is a rare disorder of glycogen metabolism complicated by neutropenia/neutrophil dysfunction. Since 2019, the SGLT2-inhibitor empagliflozin has provided a mechanism-based treatment option for the symptoms caused by neutropenia/neutrophil dysfunction (e.g. mucosal lesions, inflammatory bowel disease). Because of the rarity of GSD Ib, the published evidence on safety and efficacy of empagliflozin is still limited and does not allow to develop evidence-based guidelines. Here, an international group of experts provides 14 best practice consensus treatment recommendations based on expert practice and review of the published evidence.

We recommend to start empagliflozin in all GSD Ib individuals with clinical or laboratory signs related to neutropenia/neutrophil dysfunction with a dose of 0.3–0.4 mg/kg/d given as a single dose in the morning. Treatment can be started in an outpatient setting. The dose should be adapted to the weight and in case of inadequate clinical treatment response or side effects. We strongly recommend to pause empagliflozin immediately in case of threatening dehydration and before planned longer surgeries. Discontinuation of G-CSF therapy should be attempted in all individuals. If available, 1,5-AG should be monitored. Individuals who have previously not tolerated starches should be encouraged to make a new attempt to introduce starch in their diet after initiation of empagliflozin treatment. We advise to monitor certain safety and efficacy parameters and

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recommend continuous, alternatively frequent glucose measurements during the introduction of empagliflozin. We provide specific recommendations for special circumstances like pregnancy and liver transplantation.

1. Introduction

Glycogen storage disease type Ib (GSD Ib) is a rare inherited disorder of glycogen metabolism caused by pathogenic biallelic variants in *SLC37A4,* encoding the glucose-6-phosphate transporter (G6PT) [1,2]. Individuals with GSD Ib usually present in infancy with severe recurrent fasting hypoglycemia, hepatomegaly and impaired growth further complicated by neutropenia and neutrophil dysfunction, leading to oral and anogenital mucosal lesions, recurrent skin infections, inflammatory bowel disease, anemia and gout [1].

Since the 1990s, treatment with granulocyte-colony stimulating factor (G-CSF) has been the mainstay of therapy for neutropenia in GSD Ib individuals [3,4]. Unfortunately the clinical efficacy of G-CSF is limited [5] and the frequent subcutaneous painful injections of G-CSF represent an additional medical burden [6]. Also, the association observed in individuals with GSD1b (and other haematological conditions treated with G-CSF) and the occurrence of haematological malignancies should be taken into account [7–9].

The underlying mechanism of neutropenia and neutrophil dysfunction was only elucidated in 2019: in neutrophils, G6PT is involved in the detoxification of 1,5-anhydroglucitol-6-phosphate (1,5-AG6P) [10], which is derived from circulating 1,5-anhydroglucitol (1,5-AG). 1,5-AG6P is a potent inhibitor of hexokinases, and its' accumulation underlies the neutropenia and neutrophil dysfunction seen [10,11]. Subsequently, the use of sodium-glucose cotransporter 2 inhibitors (SGLT2i), a class of oral antidiabetic drugs, has resulted in a new pathomechanism-based treatment option. SGLT2i, such as empagliflozin, prevent the reabsorption of glucose from the urinary filtrate and enhance its urinary excretion together with 1,5-AG. Furthermore, glucose indirectly inhibits the renal 1,5-AG transporter (SGLT5, encoded by *SLC5A10*) [12,13], explaining the lower reabsorption of 1,5-AG in the kidney and its increased urinary excretion. Consequently, 1,5-AG concentration in blood is decreased following empagliflozin treatment [10].

Since 2019, empagliflozin has been used successfully in >110 GSD Ib individuals worldwide [14] and was shown to be both effective and safe. Because of the rarity of GSD Ib, the published evidence on safety and efficacy of empagliflozin is still very limited and does not allow to develop evidence-based guidelines. To collect all available experience, we have founded an international group of experts to discuss questions regarding empagliflozin treatment based on the available literature and expertise. Here, we discuss and formulate 14 best practice treatment recommendations for the treatment of neutropenia and neutrophil disfunction related symptoms in GSD Ib.

2. Methods and background

An international expert group was founded that involved all major stakeholders including pediatric and adult metabolic physicians, oncologists/hematologists, metabolic dieticians, clinical biochemists, metabolic researchers, pharmacists and patient representatives. A list of the expert group members, their professional background and experience in empagliflozin treatment of GSD Ib patients is shown in Supplementary Table 1.

Fourteen questions regarding empagliflozin treatment were formulated by the workshop leaders (SCG, TD, HM, MVdC, SW). These were circulated 6 weeks before the meeting together with all available literature retrieved by a systematic review (Supplementary Table 2, retrieved via PubMed, search date 02.01.2023, limited to English language, using the search terms “empagliflozin” “glycogen storage disease”) [14,16–27] in order to reach the 14 recommendations shown below. There is overlap in the number of published cases but at least 112 discrete GSD Ib cases were treated with empagliflozin so the total number is higher than that [14].

An expert group meeting was held on February 7–8, 2023 in Salzburg, Austria, to discuss these questions in order to develop treatment recommendations based on available evidence and expert experience. Recommendations presented are based on consensus of all participants. We used the gradation system as recommended by the American Academy of Pediatrics, with only Level C (Single or few observational studies or multiple studies with inconsistent findings or major limitations) or Level D (Expert opinion, case reports, reasoning from first principles) being applicable [28].

Of note, we choose to restrict these recommendations to the use of the SGLT2i empagliflozin as it is available worldwide and was used in all published individuals. Yet, as suggested from the preliminary data [15] from a still ongoing French study on 21 individuals, the use of dapagliflozin appears to have similar beneficial effects. It goes beyond the scope of this paper to discuss that SGLT5 was recently shown to be the renal transporter for 1,5-AG and, hence, in the future specific SGLT5 inhibitors, that may become available as drugs could work similarly but likely with a more targeted effect [12,29].

3. Background

3.1. Pharmacokinetics of empagliflozin

Empagliflozin (Jardiance®) is commercially available in the form of film-coated tablets with 10 mg or 25 mg of active ingredient [30]. By the Food and Drug Administration (FDA) empagliflozin is approved for the treatment of (1) children >10 years and adults with inadequately controlled type 2 diabetes mellitus (T2DM), in addition to diet and exercise, as monotherapy when metformin is not tolerated, or in addition to other antidiabetic agents or insulin and of (2) adults for symptomatic and chronic heart failure. The European Medicines Agency (EMA) only approves its use in adults.

Empagliflozin is rapidly absorbed after oral administration. Maximum plasma levels are usually reached within 1.5 h. Thereafter, plasma concentrations decline biphasically with a rapid distribution phase and a slow terminal phase. In diabetic individuals, it has been shown that administration of empagliflozin after ingestion of a high-fat and high-calorie meal may result in a slightly lower exposure. The terminal half-life of empagliflozin is approximately 12.4 h. Approximately 43% of the drug is excreted in the feces and 57% renally [31]. Little is known about potential off-target effects of empagliflozin, a number of non-canonical mechanisms have been proposed to explain its cardiac effects, most notably an inhibitory action on cardiac Na^+/H^+ exchanger 1 (NHE1), causing a reduction in intracellular [Na^+]. It was however shown, that NHE1 activity is not inhibited by empagliflozin. The beneficial effects of SGLT2i in failing hearts should not be interpreted in terms of actions on myocardial NHE1 or intracellular [Na^+] [32].

In T2DM, an initial dose of 10 mg empagliflozin once daily is recommended for monotherapy or combination therapy. The maximum daily dose recommended is 25 mg. In individuals with heart failure, a dose of 10 mg once daily is recommended. In diabetic individuals with a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2, the dose should not exceed 10 mg, and empagliflozin therapy is not recommended for GFR <30 ml/min/1.73 m^2. The same will likely apply to GSD Ib individuals with renal failure. In people with heart failure, with or without T2DM, treatment with empagliflozin may be initiated or continued down to a GFR of 20 ml/min/1.73 m^2. In individuals with a lower GFR, or with end-stage renal disease and/or on dialysis, the use is not recommended due to insufficient data.

No dose adjustment is required for individuals with hepatic impairment.

A pediatric phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents ≥10 to <18 years of age with T2DM mellitus [33]. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Empagliflozin has not yet been investigated in children <10 years.

3.2. Side effects of empagliflozin

The following side effects are common (≥1/100 to <1/10) to very common (≥1/10) according to the drug information [30]: genital infections; urinary tract infections (including pyelonephritis and urosepsis); hypoglycemia; thirst; constipation; pruritus, rash; volume depletion; increased urination; increased serum lipid concentrations. Less common side effects include ketoacidosis, urticaria, angioedema, dysuria, tubulo-interstitial nephritis, increased blood creatinine, decreased glomerular filtration rate, increased hematocrit, and necrotizing fasciitis of the perineum.

The following side effects were reported in a study with 112 GSD Ib individuals (94 treatment years) [14]: level 3 hypoglycemia (18%), allergic/anaphylactic reaction (1%), fungal urogenital infection (3%), urinary tract infection (7%), skin rash (3%), pruritus (1%), ketoacidosis (1%), lactic acidosis (5%), and dehydration (1%). Of note, given that hypoglycemia as well as lactic acidosis are also typical clinical symptoms of GSD Ib it is obviously difficult to establish the cause. In general, the safety profile of empagliflozin in GSD Ib seems superior or at least comparable to that in T2DM, however the limited number of treated GSD Ib cases has to be taken into account.

4. Workshop results: recommendations

An overview of all publications on empagliflozin use in individuals with GSD Ib is given in Supplementary Table 2.

4.1. When should empagliflozin treatment be started in an individual with GSD Ib?

Evidence from literature (EFL): All information available in the literature is based on treatment of symptomatic/neutropenic individuals. No reports on pre-symptomatic treatment in children or adults have been published so far. Nineteen GSD 1b infants have already been treated within the first year of life with good outcome, in some of whom empagliflozin was the first line treatment, instead of G-CSF (personal communication SBW, manuscript in preparation).

4.1.1. Recommendation 1 (grade D)

We recommend to start empagliflozin treatment in all genetically confirmed GSD Ib individuals

- with clinical or laboratory signs related to neutropenia/neutrophil dysfunction
- that are suspected to become symptomatic with respect to family history
- before surgical interventions that may occur relatively more often in the GSD 1b population, such as placement of a percutaneous endoscopic gastrostomy (PEG) tube, or liver transplantation
- with a dependence to daily G-CSF therapy to control either oral or systemic infections

In the rare cases of (adult) individuals without clinical symptoms of neutrophil dysfunction or neutropenia, there is currently no evidence to start empagliflozin treatment.

4.2. What should the empagliflozin starting dose be?

EFL: The median dose used in published cases was 0.35 mg/kg/d with (median dose in adults 0.3 mg/kg/day, median dose in children 0.4 mg/kg/day, range in all individuals 0.1–0.9 mg/kg/day) [14]. No data on correlations of the empagliflozin dose with treatment outcomes (efficacy) and side effects are currently available.

4.2.1. Recommendation 2 (grade C)

We recommend to start empagliflozin treatment with a dose of 0.3–0.4 mg/kg/d. The dose should then be titrated dependent on the individual response and possible side effects in 0.05 mg steps. In children and adolescents >10 years of age, a starting dose of 10 mg/day seems reasonable [33].

4.3. How to best take the prescribed daily dose of empagliflozin (one single dose versus two half-doses)?

EFL: No data are available on pharmacokinetics of empagliflozin in children <10 years of age. In adults, the terminal half-life of empagliflozin is approximately 12.4 h [30]. About 45% of individuals treated so far, received a single dose per day, while in the remainder, the dose was given in two halves [14]. No obvious impact of the frequency of dosing was seen on outcome and side effects. In particular, hypoglycemia was not more common in individuals with a single dose per day [14]. In few individuals, in which treatment was started with a single dose per day, twice daily dosing was later implemented either due to inconsistent glucosuria seen over a 24 h period, or because of hypoglycemia [17,22].

4.3.1. Recommendation 3 (grade C)

We recommend to start with one single dose of empagliflozin per day and split the dose in two if:

- the individual has persistent glucose homeostasis problems/hypoglycemias,
- has no persistent glucosuria over a 24-h period (dipstick testing), or
- dependent on the clinical response (persistent diarrhea, mucosal lesions, etc).

4.4. Can empagliflozin be started in an outpatient setting?

EFL: Empagliflozin has been started in an outpatient setting in >30 individuals (both children and adults) [14].

4.4.1. Recommendation 4 (grade C)

Because of the higher risk of hypoglycemia it is recommended to start treatment in an inpatient setting in:

- nonverbal children,
- individuals with a relatively short fasting tolerance, and
- individuals that chose to start taking empagliflozin in the evening. In this case, CGM is highly recommended for overnight glucose monitoring.

4.5. When should empagliflozin be given?

EFL: There is no evidence from the literature concerning the optimal timing of empagliflozin administration with respect to meals or cornstarch intake. Maximum plasma levels of empagliflozin are usually reached within 1.5 h after intake [30], but the pharmacokinetics and pharmacodynamic response may vary and depend on age [34,35]. Different dosing regimen have been successfully used, including one single morning dose, one single evening dose or split doses 1/2–1/2 or 2/3–1/3.

4.5.1. Recommendation 5 (grade D)

In general, taking empagliflozin approximately one hour after breakfast or after the morning cornstarch dose is recommended ensuring to have the maximum concentration of empagliflozin in the body present during daytime, when the individual is awake and young preverbal children can be safely supervised. The workshop participants agreed that the risk of hypoglycemia needs especially to be considered in individuals on continuous feeds due to an otherwise uncontrollable glucose homeostasis. And the timing of cornstarch intake may also be relevant as well as the individuals fasting tolerance.

Given the increased urination and thirst as the main (side) effects of empagliflozin an evening administration could likely affect the night rest/sleep and increase the risk of bed-wetting. In individuals where it was chosen to split the daily dose in two administrations, this has to be taken into account.

4.6. What are the reasons to increase the empagliflozin dose?

EFL: There is no evidence from literature. The decision to increase the empagliflozin dose has to be made on an individual basis and the combination of clinical symptoms and laboratory findings should be taken into account. It is also noteworthy that empagliflozin and G-CSF might have synergistical effects, i.e. for wound healing, as under empagliflozin, G-CSF may increase the number of better functioning neutrophils, following the decrease of 1,5-AG in blood due to empagliflozin treatment. Indeed, these neutrophils accumulate less 1,5-AG6P when individuals are on empagliflozin treatment [17,29]. PEG tubes are usually better tolerated by GSD Ib individuals on empagliflozin treatment. To prevent impaired wound healing, combined G-CSF and empagliflozin administration can be considered for few days after implementation of a PEG tube.

4.6.1. Recommendation 6 (grade D)

Possible reasons for increasing the dose of empagliflozin comprise:

- inadequate clinical treatment response (mucosal lesions, chronic diarrhea/IBD etc.)
- PEG problems (infection, excessive granulation)
- need for wound healing (e.g. after elective surgery, cave: consider to pause empagliflozin before and during surgery because of the risk of ketoacidosis).
- adaptation to weight gain, particular during growth.

We do not recommend to increase the empagliflozin dose:

- in case of neutropenia without clinical signs of neutrophil dysfunction
- based on laboratory markers in individuals with satisfactory clinical response

Of note, individuals should be treated with the lowest necessary dose and we advise to increase with 0.05 mg/kg/d steps.

4.7. What are the reasons to decrease the empagliflozin dose?

EFL: In published cases, reduction of the empagliflozin dose has mainly been reported due to hypoglycemia [22].

4.7.1. Recommendation 7 (grade D)

Reduction of the empagliflozin dose may be necessary:

- in case of recurrent hypoglycemia/decrease of metabolic control
- in case of side effects, such as empagliflozin-induced hypertriglyceridemia etc.
- in case of renal insufficiency
- as adaptation to weight changes
- in case of pregnancy (see below)

For individuals with recurrent urinary tract infections under empagliflozin treatment we recommend diagnostics for e.g. underlying predisposing anatomical variations and rather recommend prophylactic antibiotic treatment than a dose reduction of empagliflozin. For individuals with recurrent genital infections we rather recommend topical standard treatment than a dose reduction of empagliflozin. Of note, individuals should be treated with the lowest necessary dose and we advise to decrease with 0.05 mg/kg/d steps.

4.8. When should empagliflozin treatment be paused?

EFL: Pharmacokinetic studies show that a short interruption of empagliflozin treatment for few days does not result in an immediate increase in 1,5-AG6P levels (unpublished data, MVdC). Empagliflozin treatment is associated with the risk of ketoacidosis. It is unknown whether the risk of ketoacidosis is decreased under empagliflozin in individuals with a disorder that is associated with hypoketosis, such as GSD Ib. Anecdotal cases with severe keto- and lactic acidosis and dehydration in individuals with GSD Ib under empagliflozin treatment have been reported, mainly in the setting of gastrointestinal infections [14]. These episodes may be life-threatening. Given the risk of ketoacidosis in individuals with T2DM and pharmacokinetic data in healthy subjects (e.g., on average, glucosuria resolves 3 days after a single empagliflozin dose of 10 mg and 25 mg), FDA guidelines recommend considering temporarily discontinuing empagliflozin for at least 3 days prior to surgery [36].

4.8.1. Recommendation 8 (grade D)

We strongly recommend to pause empagliflozin immediately in case of gastroenteritis (vomiting/ acute diarrhea), febrile infections or threatening dehydration. This has to be communicated well with individuals/caretakers/medical team when empagliflozin treatment is started.

There is no need to interrupt empagliflozin treatment for minor surgery/short anesthesia. For large operations/long anesthesia and postoperative recovery, that are associated with a high risk of dehydration or unstable fluid homeostasis, or metabolic instability, empagliflozin treatment should be paused at least 3 days in advance.

4.9. When should G-CSF treatment be tapered/ stopped?

EFL: About half of the GSD Ib individuals published so far could stop G-CSF treatment after initiation of empagliflozin therapy [14]. It is to be expected that this value will increase as follow-up times are short in published individuals and perhaps physicians and individuals or families were initially hesitant to stop G-CSF. Usually, the 1,5-AG level in blood lowers reaching a new baseline within 2 weeks after start of treatment associated with clinical improvement in the same time frame [17].

It is important to note, that many individuals can remain (severely) neutropenic under empagliflozin despite excellent clinical response. This could be explained by the observation that neutrophils from GSD Ib individuals treated with empagliflozin still accumulate several-fold more 1,5-AG6P compared to neutrophils from healthy controls [17,29]. Most likely, this reduction in 1,5-AG6P allows for neutrophils from GSD Ib individuals to function better under empagliflozin treatment (explaining the clinical response), but in some individuals this may not be sufficient to prevent neutropenia.

4.9.1. Recommendation 9 (grade D)

Discontinuation of G-CSF therapy should be attempted in all individuals, especially because of the association of myelodysplastic syndrome and leukemia in individuals with neutropenia due to GSD 1b or other haematological disorders treated with G-CSF. We recommend considering to begin tapering G-CSF treatment 2 (−4) weeks after start

of empagliflozin, especially if the neutrophil count is normal. The same applies to neutropenic individuals in whom improvement of neutropenia related clinical signs and symptoms is observed.

Single and mostly mild oral lesions may still be present under empagliflozin treatment and usually do not require G-CSF supplementation as long as they do not impair food intake.

4.10. Should 1,5-AG or 1,5-AGP be measured routinely?

EFL: 1,5-AG can be influenced by diet or medication, gender and race, especially severe renal disease and various pathological conditions [39]. In T2DM it has become a validated marker of short-term glycemic control [40,41].

The determination of 1,5-AG in blood/plasma is not commercially available in many countries and is often done in laboratories that measure it as part of their research practice. The determination of 1,5-AG in dried blood spot (DBS) has recently become available [42]. This should facilitate the follow-up of 1,5-AG and help to evaluate the response to treatment particularly when this is suboptimal.

GSD Ib individuals treated with empagliflozin usually lower their 1,5 AG levels 5- to 6-fold to approximately 30–50 μmol/l blood, however, despite a significant decrease, some individuals remained with higher concentrations [17,19,21,22,24,26]. It is of note that GSD Ib individuals with poor metabolic control can have low 1,5-AG concentrations due to renal impairment (specifically renal tubular dysfunction).

While there is surely a correlation of 1,5-AG levels and clinical symptoms, exact data and reference ranges are not yet available and thus this topic warrants further research.

4.10.1. Recommendation 10 (grade D)

We recommend that, if available, 1,5-AG should be monitored in individuals with GSD Ib under empagliflozin treatment, particularly now that a method to measure 1,5-AG in DBS has become available. Apart from comparing metabolite concentrations among individuals, this might be helpful for longitudinal monitoring of 1,5-AG in particular individuals and help to establish correlations of 1,5-AG levels and clinical symptoms. In healthy individuals, the concentration of 1,5-AG measured in blood is around 150 μmol/L [43]. However, GSD Ib individuals often have higher values (up to 3-fold higher) presumably as a result of the large amounts of starch in their diet. Once on empagliflozin, the 1,5-AG concentration falls to new baseline levels around 50 μM [17,19,21,22,24,26]. However, in some cases, the blood concentration of 1,5-AG that is reached on empagliflozin treatment may be either higher or lower, depending on how efficiently 1,5-AG is excreted in urine. When there is a tendency of 1,5-AG to increase above the base line, this might indicate a need for adjusting the daily dose of empagliflozin.

4.11. What impact does empagliflozin treatment have on the tolerance of different starches?

EFL: Before the introduction of empagliflozin, many GSD Ib individuals showed suboptimal tolerance of different starches (e.g. uncooked cornstarch, Glycosade®), presumably due to gastrointestinal problems or IBD. Many individuals reported an improvement of IBD under use of empagliflozin that also resulted in a better tolerance of starch therapy [6].

4.11.1. Recommendation 11 (grade D)

Individuals who have previously not tolerated starches should be encouraged to make a new attempt to introduce starch in their diet after initiation of empagliflozin treatment.

4.12. Once on empagliflozin treatment, should individuals discontinue additional approaches for the treatment of neutropenia/neutrophil dysfunction?

EFL: Vitamin E has been shown to improve neutrophil count and reduce frequency and severity of infections in individuals with GSD Ib [44]. Additionally, treatment with probiotics has been widely used to address gastrointestinal symptoms [45]. GSD Ib individuals with IBD used to receive standard treatment of IBD including local steroids, 5-aminosalicylic acid (5-ASA) and adalimumab.

The value and/or necessity of these treatment approaches will need reconsideration when more data on empagliflozin treatment becomes available.

4.12.1. Recommendation 12 (grade D)

We recommend to consider discontinuing all additional treatments addressing neutropenia and neutrophil dysfunction such as vitamin E supplementation in clinically symptom-free individuals. IBD symptoms may resolve on empagliflozin therapy so that specific therapies for IBD could be tapered and/or discontinued [46].

4.13. Which parameters should be measured before the start of empagliflozin treatment and used for monitoring? At which time intervals?

EFL: Clinical features for monitoring can be derived from the published guideline papers [47,48], whereas numerous tools are available to quantify patient-reported outcome measures (PROMs) [49]. Markers for both glycemic and metabolic control may relate to both efficacy and safety. In few individuals, effects of empagliflozin on 1,5-AG levels in plasma and sometimes 1,5-AG6P in neutrophils or white blood cells were investigated [17,19–21,23,24,26]. Yet, there are only few laboratories that measure these metabolites in daily clinical practice or in their research practice, explaining why many individuals have been treated without documenting the impact of empagliflozin on the concentration of 1,5-AG in blood. For this reason, recommendations are based on expected effects and side-effects of empagliflozin. Of note, a review of the literature suggests that people with T2DM with low C-peptide level may be at increased risk of ketoacidosis, particularly if they are on statins and diuretics due to hypokalemia and impaired release of insulin [50]. More studies are warranted to further clarify these mechanisms, and evaluate the situation in individuals with GSD Ib.

4.13.1. Recommendation 13 (grade D)

We recommend to determine the following monitoring parameters.

Safety parameters:

- kidney tests including GFR (empagliflozin dose adaptation required in case of renal dysfunction)
- glucose monitoring (see recommendation 14 for details)

Efficacy parameters:

- full blood count (including neutrophil count, red blood cell count, hemoglobin, MCV and MCH, platelets)
- C-reactive protein
- erythrocyte sedimentation rate
- iron and iron binding capacity
- albumin
- 1,5-AG concentration in blood (if possible/available)
- urine dipstick/analysis for glucosuria (twice daily during first 3 days)
- uric acid
- Crohn's Disease Activity Index or Pediatric Crohn's Disease Activity Index for assessment of IBD [51,52]

Assessment of metabolic control does not differ from GSD Ib individuals that are not on empagliflozin treatment and usually includes

liver function tests, glucose monitoring, uric acid, lactate, (fasting) lipid profile, and urine analysis for proteinuria and microalbuminuria [48].

As documented in imaging studies, splenomegaly was described in about 50% of GSD Ib individuals prior to G-CSF treatment [3,4,7], and G-CSF can further increase splenomegaly. Empagliflozin treatment is not expected to have a negative effect on spleen or liver size and, therefore, imaging apart from normal follow-up of GSD Ib is not routinely indicated.

Assessment of the above-mentioned parameters is recommended at the following time points:

- Before start of empagliflozin treatment: all parameters
- 1 week after start: full blood count, urine dipstick twice daily to check for persistent glucosuria
- 4–6 weeks after starting treatment: all parameters
- after that: every 3–6 months (as part of regular GSD Ib follow up and upon clinical indication)

We do not consider neutrophil function tests necessary before starting or for monitoring of treatment with empagliflozin. Ketone monitoring is also not considered essential apart from clinical indication such as dehydration. Further studies aiming to establish a target range for 1,5-AG and/or 1,5-AG6P and make this parameter available to all individuals are needed, since this could contribute to evaluate the response to treatment and allow intervention when the clinical response is unexpected. However, all participants agree that empagliflozin use should be adapted to clinical response.

4.14. Is continuous glucose monitoring (CGM) required during introduction of empagliflozin?

EFL: Hypoglycemia is the most common effect of empagliflozin in individuals with GSD Ib and has been reported in about 18% of individuals on empagliflozin treatment in the literature [14]. Due to the nature of GSD Ib it is impossible to distinguish if hypoglycemia is related to the GSD Ib or to empagliflozin treatment.

Also, the workshop participants recognize that effects on glucose homeostasis may differ among individuals. Both increase and decrease in carbohydrate requirements and body mass index (BMI) have been reported while on empagliflozin treatment. While the increase in carbohydrate requirements can be explained by the renal loss of glucose, a decrease may also occur in individuals with previously severe IBD, in whom empagliflozin treatment results in better intestinal absorption after improvement of IBD. For an increasing number of individuals, CGM already belongs to the standard of care [53].

4.14.1. Recommendation 14 (grade D)

For safety reasons, we recommend using CGM or alternatively frequent capillary glucose measurements in all GSD Ib individuals during the introduction of empagliflozin. Special caution should be paid to young (nonverbal) children and individuals with severe IBD due to the higher risk of hypoglycemia.

We consider optimizing metabolic control a prerequisite before the start of empagliflozin treatment, e.g. to avoid that recurrent hypoglycemia, because of an instable metabolic situation, is erroneously attributed to empagliflozin and leads to unnecessary cessation.

5. Compounding of empagliflozin

Empagliflozin is available as tablets of 10 and 25 mg. The tablets can be divided, and enteral tube administration via feeding tube is possible after grinding of tablets and suspension in water. There is no stability data for liquid formulations available and hence we recommend to make capsules with the requested dosage of empagliflozin, if necessary. To produce capsules, empagliflozin tablets are crushed and grinded in a mortar. The coating of the tablets is grinded as well as possible and is left in the powder. The powder is transferred to a measuring cylinder. Then lactose monohydrate is added to reach the needed volume to fill the batch of capsules. The mixture is transferred to the mortar again and blended for at least five minutes. The resulting powder mixture is then filled into the capsule shells. The capsules can be taken orally or opened by the parents and the powder can be mixed with water and given on a spoon or via a tube.

5.1. Additional notes on special circumstances

5.1.1. The use of empagliflozin in pregnancy

EFL: Empagliflozin has been used in one GSD Ib individual during pregnancy with good success and no obvious adverse effects [18]. In animal studies, a recent systematic review of all available data [54] on the offspring effects of SGLT2i during pregnancy and lactation found that SGLT2i were generally safe during the first trimester. However, exposure during postnatal day 21 to 90 in juvenile rats, a period coinciding with the late second and third trimester of human renal development, caused dilatation of the renal pelvis and tubules. Human data evaluated consisted of a pharmaceutical database of inadvertent pregnancies during SGLT2i use, which found an increase in miscarriages and congenital malformations. In animal studies SGLT2i were excreted in breast milk and affected neonatal growth, but human data are not available. Based on these findings we advise to consider to discontinue SGLT2i during pregnancy and lactation.

5.1.2. The use of empagliflozin in GSD Ib individuals undergoing/after liver transplantation (LTX)

The immunological effect of empagliflozin for GSD Ib individuals could make LTX accessible to a larger group of individuals, for which additional considerations to recommendation 8 for pausing empagliflozin apply. After LTX for GSD Ib, strict dietary treatment can be abandoned, and it was recently shown that the concentration of 1,5-AG in blood decreased after LTX [37], presumably due to the cessation of the starch treatment. Yet, neutropenia persists, since the neutrophils continue to be deficient in G6PT and still accumulate toxic 1,5-AG6P. Hence, empagliflozin treatment needs to be continued after LTX, but the moment of restarting needs to be individualized. It is possible that corticosteroid-induced glycosuria contributes to lower 1,5-AG concentrations postoperatively. The half-removal time of healthy neutrophils has been estimated 5.4 days [38]. This does not necessarily mean that the neutrophils have died, because they are capable of chemotaxis and migration to other tissues and organs. On the other hand, in individual GSD Ib cases, even under empagliflozin, the lifespan of neutrophils may be lower. Therefore, consideration should be given to restarting or increasing the dose of G-CSF perioperatively.

6. Conclusion

Here we collected published evidence and expert opinions based on real life data from the last four years after the first scientific paper describing successful off-label use of empagliflozin in GSD Ib individuals. We hereby aim to standardize the use of empagliflozin in GSD Ib. The story of empagliflozin is a perfect showcase of repurposing a drug that is registered for a common acquired disorder for an inherited orphan disease designation. Challenges are still being encountered at the level of reimbursement and legal issues, among others. Historical guidelines and care pathways have defined the parameters that can be used for monitoring GSD Ib individuals, but do not include novel applications, such as CGM. A standard set of outcomes for GSD individuals that includes these novel techniques of management and monitoring as well as PROMs is under development, to improve healthcare and research, as innovative treatments are increasingly under investigation. The current recommendations need regular revisions e. g. after 3–5 years. The process of drug repurposing using SGLT2i for people with GSD Ib and our current recommendations answer prioritized questions

from the recent liver GSD knowledge agenda [55]. The new uncertainties associated with the SGLT2i treatment in GSD Ib will drive future research.

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Author contributions

Conceptualization, workshop design/workshop preparation and -leading: MVDC; TGJD; SCG; HM; SBW. Data curation, formal analysis and interpretation: all authors. Funding acquisition, methodology, project administration, resources, software, supervision, validation: SCG; SBW. Writing original draft of the article: SCG; SBW. Revising it critically for important intellectual content, editing: all authors.

Ethics declaration

Not applicable.

Declaration of competing interest

All authors with exception of ELC, JlF, PH and SKU received accommodation support by Sophie's Hope Foundation. All authors report no conflict of interest related to this study.

TGJD declares that he has confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical Inc, ModernaTX Inc., and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone), and participations in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc, ModernaTX Inc., and Beam Therapeutics). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG.

ND declares that he is a director and minority shareholder in SpOtOn Clinical Diagnostics Ltd. KMS declares that in the last 36 months there were consultancy agreements with BioMarin, Chiesi, Takeda, Sanofi, Amicus and Immusoft Corporation.

SCG declares that over the last 3 years in the area of inherited metabolic diseases she has received accommodation support from Nutricia Metabolics, honoraria for lectures from Vitaflo and Ultragenyx, and that she is an advisory board member of Ultragenyx.

JL and BS declare no conflict of interest. Funding to Sophie's Hope Foundation and curegsd1b.org is by individual donors, rather than pharmaceutical or medical food industry.

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HM declares that over the last 3 years in the area of inherited metabolic diseases she has received accommodation support from Vitaflo. honoraria for lectures from Vitaflo and Nutricia and served as a paid consultant for Ultragenyx.

SBW declares that over the last 3 years in the area of inherited metabolic diseases she has received accommodation support from Nutricia Metabolics.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2024.108144.

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