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BRIEF REPORT

# Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire

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ABSTRACT

**Purpose:** This paper aims to report collective information on safety and efficacy of empagliflozin drug repurposing in individuals with glycogen storage disease type Ib (GSD Ib).
**Methods:** This is an international retrospective questionnaire study on the safety and efficacy of empagliflozin use for management of neutropenia/neutrophil dysfunction in patients with GSD Ib, conducted among the respective health care providers from 24 countries across the globe.
**Results:** Clinical data from 112 individuals with GSD Ib were evaluated, representing a total of 94 treatment years. The median age at start of empagliflozin treatment was 10.5 years (range = 0-38 years). Empagliflozin showed positive effects on all neutrophil dysfunction–related symptoms, including oral and urogenital mucosal lesions, recurrent infections, skin abscesses, inflammatory bowel disease, and anemia. Before initiating empagliflozin, most patients with GSD Ib were on G-CSF (94/112; 84%). At the time of the survey, 49 of 89 (55%) patients previously treated with G-CSF had completely stopped G-CSF, and another 15 (17%) were able to reduce the dose. The most common adverse event during empagliflozin treatment was hypoglycemia, occurring in 18% of individuals.
**Conclusion:** Empagliflozin has a favorable effect on neutropenia/neutrophil dysfunction–related symptoms and safety profile in individuals with GSD Ib.



## Introduction

Glucose-6-phosphate translocase (G6PT) (*SLC37A4,* OMIM 602671) shuttles glucose-6-phosphate from the cytosol to the endoplasmic reticulum where it is hydrolyzed by glucose-6-phosphatase for energy production. G6PT is expressed ubiquitously, and its deficiency causes glycogen storage disease type Ib (GSD Ib) (OMIM 232220), a rare autosomal-recessive inborn error of carbohydrate metabolism causing fasting hypoglycemia, hepatomegaly, neutropenia, and neutrophil dysfunction.[1-5]

1,5-anhydroglucitol-6-phosphate (1,5-AG6P) is a structural analog of glucose-6-phosphate.[6] Deficiency of G6PT results in failure to eliminate 1,5-AG6P, and its accumulation within granulocytes leads to energy deficit and subsequent apoptosis.[6] This toxicity explains the neutrophil dysfunction and neutropenia in GSD Ib, associated with serious infections, inflammatory bowel disease (IBD), and painful mucosal lesions throughout the entire gastrointestinal tract.

The elucidation of this pathogenetic mechanism in 2019 implicated a treatment option.[6] SGLT2 inhibitors, such as

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empagliflozin, are antidiabetic drugs that inhibit renal glucose reabsorption, thus causing glucosuria. Glucosuria decreases renal 1,5-anhydroglucitol (1,5-AG) reabsorption and thereby lowers its serum concentration.[7] Individual treatment of 6 patients with GSD Ib with empagliflozin has shown very promising results with respect to IBD, ulcerative stomatitis, wound healing, and anemia.[8-11]

Many scientific and regulatory hurdles need to be overcome in translating experimental studies to clinical application. After 2019 and despite the COVID-19 pandemic, off-label empagliflozin treatment in individuals with GSD Ib spread virally via both the extremely well-connected patient community and health care providers. To report collective information on safety and efficacy of empagliflozin drug repurposing in GSD Ib, we performed this questionnaire study among health care providers. Our observations reflect real-world, life-changing experiences in 112 individuals with GSD Ib and summarize the outcome, safety, and efficacy of this novel treatment.

## Materials and Methods

Consent to off-label treatment with empagliflozin was obtained from the patients or parents/legal guardians by the treating health care providers. This is a retrospective data collection of anonymized data collected during regular patient care for which, in line with the Declaration of Helsinki,[12] neither individual patients' consent nor formal research ethics committee approval was required. Authors at institutions that required patient consent for the questionnaire study were responsible to obtain this permission from the patient or guardian.

After scientific presentations about the use of empagliflozin for GSD Ib at the Society for the Study of Inborn Errors of Metabolism and the International Glycogen Storage Disease 2019 conferences, in collaboration with the European Reference Network for Hereditary Metabolic Disorders, United for Metabolic Diseases, and multiple patient organizations, a Zoom webinar was organized on September 15, 2020 to share clinical and personal experiences of empagliflozin treatment in patients with GSD Ib. Meanwhile, on request, a written protocol was provided on management and monitoring (see Supplemental Material A). All participating health care providers were invited to collectively share clinical experiences by a SurveyMonkey® web-based questionnaire that was sent on July 15, 2021. Preliminary results were discussed in a Zoom meeting on September 27, 2021, and the survey was closed on October 17, 2021.

The questionnaire consisted of 29 questions exploring patient demographics, details on use of empagliflozin and G-CSF, clinical findings both before starting empagliflozin and on follow-up after starting, and adverse events (AEs) (see Supplemental Material B).

## Results

Data on 112 individuals with GSD Ib from 24 different countries on 6 continents were included in this study. The median age at start of empagliflozin treatment was 10.5 years (mean [range] = 12.8 [0-38] years); 71% of the individuals were younger than 18 years. Not all data were available for all patients; data are therefore presented as x/*n* available.

Our data comprise information on a total of 94 treatment years. The median duration of treatment was 9.5 months (mean [range] = 10.1 [<1-27] months). The median empagliflozin dose was 0.35 mg/kg body weight/day (median adults = 0.3 mg/kg/day, median children = 0.4 mg/kg/day, range [both groups] = 0.1-0.9 mg/kg/day). Overall, 43% of individuals (48/112) received a single dose per day, whereas in the remainder, empagliflozin was given twice daily. In 70% of individuals (78/112; individuals <18 years, 63/80 [79%] and >18 years, 15/32 [47%]), empagliflozin was started in an inpatient setting.

In most patients (78%, 85/109), the costs of empagliflozin treatment were reimbursed (mainly by health insurance, the national health system, or the hospital).

Positive effects of treatment were observed for all neutropenia-associated symptoms (Table 1). There were no major differences in outcome or AEs between pediatric and adult individuals (Tables 1 and 2) or between patients receiving 1 single dose vs 2 half doses of empagliflozin per day.

Before starting empagliflozin, 84% of the individuals (94/112) were treated with G-CSF (median [range] dose = 4.1 [0.4-15.0] µg/kg/day). Of note, in 2 patients, G-CSF was stopped in the weeks before starting empagliflozin, and these individuals were counted as having G-CSF before starting. In the G-CSF–treated patients, the most frequently reported treatment dosages/regimens were daily (52/84), 3×/week (12/84), 2×/week (10/84), every second day (5/84), and intermittent (5/84). Data on G-CSF use after the initiation of empagliflozin treatment were available for 107 patients because for 3 patients, follow-up was too short. Of these 107 individuals, 89 were on G-CSF before starting empagliflozin. Of these, 49 of 89 (55%) individuals had completely stopped G-CSF at the time of the survey, and in 15 of 89 (17%) individuals, the G-CSF dose could be significantly reduced. Information on when G-CSF treatment was discontinued is available for 46 of 49 patients: in 11 patients, G-CSF was stopped immediately; in 8 patients, within 0 to 2 weeks; in 11 patients, within 2 to 4 weeks; in 5 patients, within 5 to 8 weeks; in 3 patients, within 9 to 12 weeks; in 2 patients each, within 4 and 5 months; and in 1 patient each, after 6, 7, 8, and 15 months.

An AE is defined as any unfavorable and unintended event that is observed after administration of a pharmaceutical product. In 77 patients (69%), no AEs were reported; for 23 patients, 1 AE was reported (20.5%); for 6 patients (5%), 2 AEs were reported; and for 3 patients (3%), 3 AEs were reported (Table 2).

**Table 1** Clinical findings before and during use of empagliflozin

| Clinical/Laboratory Findings | Before Empagliflozin | | | During Empagliflozin | | |
|---|---|---|---|---|---|---|
| | All | Individuals <18 y | Individuals >18 y | All | Individuals <18 y | Individuals >18 y |
| Neutropenia | | | | | | |
| Severe (ANC <500/μL) | 29% (32/112) | 30% (24/80) | 25% (8/32) | 10% (11/108) | 12% (9/76) | 6% (2/32) |
| Moderate (ANC 500-1000/μL) | 41% (46/112) | 41% (33/80) | 40% (13/32) | 22% (24/108) | 20% (15/76) | 28% (9/32) |
| Mild (ANC 1000-1500/μL) | 13% (15/112) | 14% (11/80) | 13% (4/32) | 15% (16/108) | 15% (11/76) | 16% (5/32) |
| No | 17% (19/112) | 15% (12/80) | 22% (7/32) | 53% (57/108) | 54% (41/76) | 50% (16/32) |
| Recurrent oral/anogenital mucosal lesions | 68% (76/112) | 69% (55/80) | 66% (21/32) | 13% (14/109)[a] | 17% (13/78) | 3% (1/31) |
| Recurrent bacterial/ skin infections | 54% (61/112) | 50% (40/80) | 66% (21/32) | 8% (9/109)[a] | 9% (7/78) | 6% (2/31) |
| IBD | | | | | | |
| Severe | 10% (11/110) | 10% (8/78) | 9% (3/32) | 0% (0/106) | 0% (0/76) | 0% (0/30) |
| Moderate | 27% (30/110) | 26% (20/78) | 31% (10/32) | 6% (6/106) | 5% (4/76) | 7% (2/30) |
| Mild | 23% (25/110) | 24% (19/78) | 19% (6/32) | 16% (17/106) | 17% (13/76) | 13% (4/30) |
| No | 40% (44/110) | 40% (31/78) | 40% (13/32) | 78% (83/106) | 77% (59/76) | 80% (24/30) |
| Anemia | | | | | | |
| Requiring red blood cell transfusions | 4% (5/112) | 5% (4/80) | 3% (1/32) | 0% (0/110) | 0% (0/78) | 0% (0/32) |
| Requiring iron therapy | 37% (41/112) | 35% (28/80) | 40% (13/32) | 16% (18/110) | 15% (12/78) | 19% (6/32) |
| Requiring no intervention | 32% (36/112) | 31% (25/80) | 72% (23/32) | 14% (15/110) | 18% (14/78) | 3% (1/32) |
| No | 27% (30/112) | 29% (23/80) | 22% (7/32) | 70% (77/110) | 67% (52/78) | 78% (25/32) |
| G-CSF treatment | 84% (94/112) | 80% (64/80) | 88% (28/32) | 37% (40/107) | 42% (32/75) | 25% (8/32) |
| Median dose, μg/kg/day | 4.0 | — | — | 1.7 | — | — |
| Daily dose | 52/110 | — | — | — | — | — |
| 3×/week | 12/110 | — | — | — | — | — |
| 2×/week | 10/110 | — | — | — | — | — |
| Every second day | 5/110 | — | — | — | — | — |
| Intermittent | 5/110 | — | — | — | — | — |

*ANC*, absolute neutrophil count; *IBD*, inflammatory bowel disease.
[a]Milder, rarer, and less painful than before.

The most common AE was level 3 hypoglycemia, defined as <3.0 mmol/L (54 mg/dL) and characterized by altered mental and/or physical status requiring assistance. This occurred in 18% (20/111) of all patients; of these 20 patients, 13 of 77 (17%) started in an inpatient setting and 7 of 34 (21%) started in an outpatient setting. The dosing frequency had no impact on the frequency and risk of hypoglycemia (21% [10/48] of patients receiving a single dose of empagliflozin per day, 17% [11/64] of patients receiving empagliflozin twice daily). Hypoglycemia occurred in both pediatric ($n = 16$) and adult ($n = 4$) patients (median age of patients with hypoglycemia = 6 years, range = 0-26 years). Nine patients (8%, 8 children, 1 adult; median age = 6 years) required inpatient treatment, whereas 11 (8 children, 3 adults, median age = 8 years) required outpatient treatment for this AE.

The most severe AE was lactic acidosis, reported in 6 patients (5 children, 1 adult), of whom 5 required hospitalization (4 children, 1 adult). One of the adult individuals also had significant ketoacidosis. In 1 adult patient, 2 decompensations requiring intensive care unit observation were reported, both associated with gastroenteritis and dehydration (1 caused by norovirus, 1 unknown).

## Discussion

The SGLT2 inhibitor empagliflozin is approved for adults with type 2 diabetes mellitus, the most prevalent acquired disorder of carbohydrate metabolism. GSD Ib is an ultrarare, inherited disorder (the overall prevalence is about 1 in 1,000,000), and experimental work underlying empagliflozin treatment in GSD Ib was only very recently published.[6] The first case studies in 2020 reported successful use of empagliflozin to treat neutropenia and neutrophil dysfunction–related symptoms and signs in individuals with GSD Ib. Subsequently, the treatment gained much interest within the metabolic community and patient support groups, which now enables us to present data on 112 patients with GSD Ib treated with empagliflozin.

We demonstrate that empagliflozin leads to improvement of neutropenia and shows positive effects on all neutropenia and neutrophil dysfunction–related symptoms, including oral and urogenital mucosal lesions, recurrent infections, skin abscesses, IBD, and anemia. Whereas before start of empagliflozin treatment, 70% of patients either had severe or moderate neutropenia despite G-CSF treatment, 53% of patients achieved normal neutrophil counts on empagliflozin

**Table 2** Adverse events during empagliflozin use

| | Level 3 Hypoglycemia | Allergic/ Anaphylactic Reaction | Fungal Oral Infections | Fungal Genital Infections | Urinary Tract Infection | Skin Rash | Pruritus | Ketoacidosis | Lactic Acidosis | Dehydration |
|---|---|---|---|---|---|---|---|---|---|---|
| AE not reported, *n* (%) | 91 (82) | 111 (99) | 112 (100) | 109 (97) | 104 (93) | 109 (97) | 111 (99) | 111 (99) | 106 (95) | 111 (99) |
| AE occurred, *n* (%) | 20 (18) | 1 (1) | — | 3 (3) | 8 (7) | 3 (3) | 1 (1) | 1 (1) | 6 (5) | 1 (1) |
| AE occurred in individuals <18 y, *n* (%) | 14 (18) | 1 (1) | — | 1 (1) | 5 (6) | 2 (3) | 1 (1) | — | 3 (4) | — |
| AE occurred in individuals >18 y, *n* (%) | 6 (14) | 0 | 0 | 2 (5) | 3 (7) | 1 (2) | 0 | 1 (2) | 3 (7) | 1 (2) |
| AE requiring hospitalization, *n* (%) | 9 (8.1) | — | — | — | — | — | — | 1 (0.9) | 5 (4.5) | 1 (0.9) |
| AE requiring outpatient treatment, *n* (%) | 11 (10) | 1 (1) | — | 3 (3) | 6 (5) | 3 (3) | 1 (1) | — | 1 (1) | — |
| Median age of affected patients (y) | 6 | 37 | NA | 6 | 5 | 12 | 17 | 23[a] | 5 | 23[a] |
| Median age of patients requiring hospitalization (y) | 6 | NA | NA | NA | 2 | NA | NA | 23[a] | 6 | 23[a] |
| Median age of patients requiring outpatient treatment (y) | 8 | 37 | NA | 5.8 | 7 | 12 | 17 | NA | 6 | NA |
| Occurrence of AE per 10 treatment years | 2.1 | 0.1 | — | 0.3 | 0.8 | 0.3 | 0.1 | 0.1 | 0.6 | 0.1 |
| Treatment duration (y) until first AE occurrence | 4.7 | 94.3 | — | 31.4 | 11.8 | 31.4 | 94.3 | 94.3 | 15.7 | 94.3 |
| Prevalence | Very common | Common | NA | Common | Common | Common | Common | Common | Common | Common |

Very common: >1 in 10 (0.1 = 10%), common: 1-10 in 100 (0.01-0.1 = 1%-10%), uncommon: 1-10 in 1000, rare: 1-10 in 10,000, very rare: <1 in 10,000.

*AE*, adverse event; *NA*, not applicable.

[a]Two episodes occurred in the same patient.

treatment. At the time of data collection, 49 of 89 previously G-CSF–treated patients had stopped G-CSF after the initiation of empagliflozin; of these, 30 (61%) had stopped within the first month. It is conceivable that even more patients could stop G-CSF treatment. Potential reasons why this has not been done yet are (1) short duration of treatment/follow-up at time of data collection, (2) limited experience with empagliflozin for this indication, and (3) hesitation to stop G-CSF in case of clinical improvement but persistent (mild) neutropenia.

The efficacy of empagliflozin was similar in both pediatric and adult patients. In patients with type 2 diabetes mellitus, empagliflozin is administered once daily. Because of the risk of hypoglycemia, 57% of the patients with GSD Ib in our study received 2 half doses of empagliflozin per day. The dosing frequency appeared not to have a significant impact on efficacy. Plasma 1,5-AG concentrations have not been systematically analyzed in this patient cohort. Therefore, it is yet unknown which dosing regimen is superior in lowering the plasma concentration of this toxic metabolite.

Empagliflozin has a good safety profile in individuals with GSD Ib. Although most of the reported AEs were common, as defined by occurrence in 1 to 10 per 100 patients treated (1%-10%), mostly these were nonserious AEs and manageable in an outpatient setting. The most frequently reported AE was hypoglycemia (occurred in 18% of subjects). Hypoglycemia is a common finding in patients with GSD Ib, so it is impossible to determine from these data whether empagliflozin treatment contributed to these episodes. The same is true for lactic acidosis. Hypoglycemia was not more frequent in patients who received empagliflozin in 1 single dose per day than those who received divided dosing. Because empagliflozin is not approved for use in children, we were especially alert for AEs in younger children. We observed that the AE hypoglycemia was reported with equal frequency in both in individuals <18 years (18%) and >18 years (14%); for all other AEs, the size of the cohort is too small to draw firm conclusions. Therefore, we advise to consider initiation of empagliflozin treatment in an inpatient setting in preverbal children or in patients with GSD Ib with unstable glucose control.

Based on the observed serious AE of ketoacidosis, requiring intensive care unit treatment twice in a 23-year-old patient during gastroenteritis with dehydration, we would like to emphasize that sufficient fluid intake should generally be guaranteed. In case of fever, decreased gastrointestinal intake, acute vomiting, and/or diarrhea, the role of empagliflozin in the development of acute metabolic decompensation (eg, hypoglycemia ± lactic acidosis) and dehydration (caused by ongoing glucosuria) should be carefully balanced against risks and consequences of short-term empagliflozin discontinuation on neutropenia and neutrophil dysfunction. Effects of SGLT2 inhibition on both glucosuria and neutropenia/neutrophil dysfunction may pharmacodynamically differ. It has been observed that blood concentrations of 1,5-AG6P and 1,5-AG only decrease to a new steady state approximately 15 to 30 days after initiation of empagliflozin in patients with GSD Ib.[8] Although for decades the neutrophil lifespan has been considered a matter of hours,[13] this idea has recently been challenged, estimating a lifespan of 5.4 days.[14] Therefore, it may be safer to stop empagliflozin during intercurrent illness for 1 to 2 days in patients with GSD Ib until glucose and fluid homeostasis are secured.

This report of the clinical experience of 112 pediatric and adult individuals with GSD Ib clearly shows how SGLT2 inhibitors, among the most widely prescribed drugs for a very common acquired disease, can be repurposed to improve medical outcomes for individuals with an ultra-rare inherited disease. Several methodological limitations concerning this study should be considered. This study is retrospective, and standardized clinical and biochemical outcome parameters have not yet been defined, which made a more detailed study difficult. In addition, despite the best efforts, the authors will not have been able to include all patients with GSD Ib treated with empagliflozin to date. For individual patients with GSD Ib, these positive results should be carefully weighed against the reported AEs and the known disadvantages and complications, especially of long-term use of G-CSF, such as the risk of malignancies. Preliminary evidence suggests that empagliflozin has the potential to be become the first-line treatment for neutropenia and neutrophil dysfunction–related symptoms in individuals with GSD Ib. Future studies are warranted on the origin of 1,5-AG, long-term safety and efficacy profile of empagliflozin, pharmacokinetics/-genetics, and patient-reported outcomes in different age groups.

## Data Availability

Data are available on request.

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"CureGSD1b" (www.curegsd1b.org), a growing worldwide community with nearly 200 GSD1b patients and families.

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## Ethics Declaration

This is a retrospective collection of anonymized data collected during regular patient care, for which, in line with the Declaration of Helsinki,[12] neither individual patients' consent nor formal research ethics committee approval was required. Authors at institutions that required patient consent were responsible to obtain this permission from the patient or guardian.

## Conflict of Interest

All authors declare no conflicts of interest.

## Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2022.04.001) contains supplementary material, which is available to authorized users.

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