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Neutropenia in Glycogen Storage Disease Ib (GSD Ib): Outcomes for Patients Treated with Granulocyte Colony-Stimulating Factor (G-CSF)

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Summary

GSD Ib is a complex disorder of glucose metabolism causing severe chronic neutropenia. G-CSF is effective to raise blood neutrophil counts and reduce fevers and infections in most patients. In conjunction with other therapies (salicylates, mesalamine sulfasalazine and prednisone), G-CSF ameliorates inflammatory bowel symptoms, but doses must be limited because it increases spleen size associated with abdominal pain.

Keywords

Glycogen storage disease; granulocyte colony-stimulating factor; hypoglycemia; splenomegaly

Introduction

Glycogen storage disease type Ib is a rare metabolic disorder causing hepatomegaly, hypoglycemia and lactic acidosis. [1] Neutropenia, neutrophil dysfunction, recurrent infections and enterocolitis are additional important features. GSD Ib is caused by mutations in *G6PT1*, the gene for glucose-6-phosphate transporter, a transmembrane protein of the endoplasmic reticulum of neutrophils and other cells. [2–4] The mutations in the glucose-6-phosphate transporter impair the survival of neutrophils and also blunt their metabolic burst associated phagocytosis. [5]

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic growth factor essential for the production and maintenance of the normal supply of blood neutrophils. [6] Administered pharmacologically, it stimulates neutrophil production and accelerates their release into the blood, thereby increasing blood neutrophil counts. [7] G-CSF has anti-apoptotic effects, promoting the survival of neutrophils and primes these cells for an enhanced metabolic burst through activation of the serine-threonine kinase and STAT kinase pathways. [8] In vivo treatment with G-CSF increases glucose transport across the cell membrane, increases accumulation of cytoplasmic glycogen, and increases the production of granule enzymes and numerous other cellular proteins through changes in gene expression. [9]

In 1992, Roe, et al reported on treatment of two males with enterocolitis with colony-stimulating factors – granulocyte macrophage colony-stimulating factor (GM-CSF) and G-CSF. Both patients had adverse effects of GM-CSF and were switched long term to G-CSF with considerable benefit. [9] Subsequently, several case reports have documented the benefits and some adverse effects associated with this long term treatment. [10–12] For a better perspective on the long term benefits and adverse events associated with G-CSF, we formed a cooperative study group to review the effectiveness and long term outcomes of GSD Ib patients treated with G-CSF.

Methods

Informed Consent was obtained for this study through the Investigational Review Boards at the Connecticut Children's Medical Center, Hartford CT; Duke University Medical Center, Durham, NC; Medizinische Hochschule, Hannover, Germany; Princess Margaret Cancer Center, Toronto, Canada; and University of Washington, Seattle WA. All participating patients gave their informed consent. The patients were followed prospectively. Data for this report came from chart reviews or data submitted to the Severe Chronic Neutropenia offices in Seattle, WA and Hannover, Germany utilizing standardized forms. The analysis focused on clinical assessments, laboratory results, patterns of infections, symptoms of enterocolitis, liver and spleen size before and on G-CSF. Liver and hematopoietic transplants, development of AML and deaths were as reported to the individual centers on annual case

report forms. For consistency, all patients treated with G-CSF on an intermittent basis (every other day, three days a week or other schedules) were normalized to be expressed as micrograms/kilogram/day. Data on mutational analysis was obtained from the testing laboratories.

Results

Patients

We reviewed medical records for total of 103 patients, 47 adults (21 males, 26 females), and 56 children (under age 18, 27 males, 29 females) from the cooperating centers. (Table 1) The age range for the adults was 18 to 47 years and the children 1 to 17 years. Data available for most patients indicated that neutropenia was present at birth or soon thereafter (absolute neutrophil counts prior to G-CSF: median $0.2 \times 10^9/L$, mean $1.0 \times 10^9/L$ SEM ± 0.3 , range 0.0 to $16.3 \times 10^9/L$, Table 1). There were insufficient CBC data available to determine if neutropenia was more severe during the first years of life or changed later in life without G-CSF, but pretreatment values were the same in both children and adults. Most patients were mildly anemic (prior G-CSF, hematocrit median 32.1%, mean 33.3 %, range 23.4 to 64.2 %) and many had mild thrombocytosis (platelet counts median $463 \times 10^9/L$, mean $479 \times 10^9/L$, range 113 to $1071 \times 10^9/L$) before G-CSF. Lymphocytes and monocytes were within normal limits. For the review, we also search the literature for cases of myelodysplasia (MDS) and acute myeloid leukemia (AML) in patients with GSD Ib.

Diagnosis

In most patients, glycogen storage disease Ib was diagnosed based on clinical presentations: hypoglycemia, hepatosplenomegaly, seizures, diarrhea, neutropenia and failure to thrive. In four patients the diagnosis was based on liver biopsy, showing characteristic pattern of glycogen deposition. Twelve patients were diagnosed because they had at least one affected sibling; one patient had two affected siblings. In the families, five patients had an older sibling with GSD Ib, one patient's mother and her sibling had GSD Ib, and one patient's uncle had GSD Ib. Sequencing data for *G6PT1* were available for review for 46 patients; it revealed more than 20 different mutations. At present there is no known genotype-phenotype correlation for the severity of neutropenia or its complications in GSD Ib. [14]

G-CSF treatment

The patients started G-CSF treatment at a median age of 3.9 years, range 0.04 to 33.9 years. (Table 2) Most were started on daily or alternate-day G-CSF at doses of 1–2 mcg/kg/d with the dose gradually raised to increase neutrophil counts to the 1.0 to $2.0 \times 10^9/L$ range, while observing for rapid enlargement of the spleen or new abdominal pain. Usually a neutrophil count greater than $1.0 \times 10^9/L$ was achieved within a few weeks and the dose could be maintained at a relatively stable level for the individual patient on a long-term basis, adjusting the dosing to match changes in the patient's weight.

All patients were treated with G-CSF and achieved a median ANC of $1.2 \times 10^9/L$ (mean 2.2×10^9 SEM ± 0.2 , range 0.0 to $68.5 \times 10^9/L$). Patients were observed on G-CSF treatment for

a median duration of 10.3 years (range 0.01 to 29.3 years) with a median dose of 3.0 mcg/kg/d (range 0.01 to 93.1 mcg/kg/d). The total estimated G-CSF exposure for the population was greater than 1200 patient years.

Infections

All patients had a history of recurrent fevers and infections prior to G-CSF. The most common events were: recurrent otitis and upper respiratory infections (81%), gingivitis and mouth ulcers (69%), abscesses (53%), cellulitis (31%) and pneumonia (28%) inflammatory bowel disease (28%). The patients often had chronic abdominal pain, cramps and diarrhea associated with generalized anorexia, malnutrition and failure to thrive. These events were recurrent in most patients and interplayed with the risk of hypoglycemia and seizures. The patients also require almost continual feeding with attendant risk of aspiration, especially when a nasogastric feeding was used, and abdominal cellulitis as a complication of percutaneous feeding tubes.

On G-CSF the types of infections were unchanged, but patients and their parents and other care providers consistently report that infections were less frequent and the symptoms were less severe, as previously reported. [10–17]

Enterocolitis

As noted, enterocolitis was a consistent problem. We found that 36 of 74 patients reported symptoms of enterocolitis either before or on G-CSF. Of these patients, 21 of 74 described enterocolitis before G-CSF and 30 of 74 described symptoms of enterocolitis during G-CSF treatment, often despite other treatments, e.g. mesalamine, prednisone, sulfasalazine and adalimumab in addition to G-CSF. Although the symptoms persist, almost all patients reported some improvement with G-CSF therapy.

Pregnancy

Three women reported pregnancies. Patient #1 (gravida 2, para 2) administered G-CSF in all trimesters with the first pregnancy and in the second trimester with the second pregnancy, had two full-term infants without newborn complications. Patient # 2 (gravida 3, para 3) administered G-CSF in the second and third trimester for the first and third pregnancies and in all trimesters for the second pregnancy. The first pregnancy was a multiple birth (triplets) with delivery at 29 weeks requiring NICU support. The second and third pregnancies were full term infants without newborn complications. The third patient had a miscarriage in a pregnancy after G-CSF was discontinued and later had a successful pregnancy on G-CSF.

Adverse Events

The common side effects from injections of G-CSF were transient bone pain, headaches and arthralgias. By using low doses of G-CSF administered on a regular daily or every other day basis these adverse effects rarely limited treatment. By contrast, granulocyte-macrophage colony-stimulating factor (GM-CSF) caused severe adverse effects, limiting its use substantially. [10, 11]

Splenomegaly and Hepatomegaly

Splenomegaly was present in 33/70 (47%) prior to G-CSF and 53/70 (76%) on G-CSF, based on physical examinations and/or imaging. There was no systematically collected data on exact spleen size, but in some patients the size increased dramatically and pain and early satiety limited G-CSF treatment, as previously reported. [1, 13] This contrast markedly with other diseases treated long-term with G-CSF in whom splenic enlargement, if it occurs, is much less and comes on much more gradually. Eight GSD Ib patients, all on G-CSF, had splenectomies because of the degree of splenic enlargement or pain. In contrast to splenomegaly, the size of the liver did not appear to change on G-CSF therapy. Reports for 69/71 (97%) patients indicated an enlarged liver prior to G-CSF, decreasing to 57/71 (80%) on G-CSF.

Acute Myelogenous Leukemia

Four of the 103 patients in this observational study have developed MDS or AML. In addition there are 4 other GSD Ib patients known to have developed MDS or AML. (Table 3) One patient (# 5) was reported to develop acute AML in 1984, before availability of G-CSF. [18] The other 7 patients [3 reported cases [19–21] and 4 as yet unreported] were treated with G-CSF for 6–25 years before MDS/AML. Four of these patients had hematopoietic stem cell transplantation (2 adults, 2 children); 1 adult and one child are currently living.

Deaths

There are 13 known deaths: sepsis (8), complications of hematopoietic stem cell transplantation (2), suicide (1), cardiac arrest (1), Unknown (1).

Discussion

Glycogen storage disease Ib is a multifaceted disorder because of the effects and consequences of excessive depositions of glycogen and defective mobilization of glucose from the glycogen stores. [1–2] GSD Ib is unique because of the neutrophil's requirement for a rapid and sustained increase in energy for the characteristic metabolic burst associated with the cell's engagement with microorganism or cytokines initiating the cell's metabolic burst. [3, 22] The critical event is the failure of the cells to mobilize glucose through the endoplasmic reticulum because of the deficiency of the glucose-6-phosphate transporter. Interestingly, a second disorder of glucose transport through the endoplasmic reticulum caused by mutations in *G6PC3*, i.e., mutation G6Pase- β , also causes neutropenia without the clinical features of a glycogen storage disease. [23]

This collaborative study was conducted to assess the long-term benefits and risks of G-CSF treatment. We observed that neutropenia is a very consistent feature of GSD Ib and that all patients appear to respond to G-CSF in a dose-dependent manner, most responding to relatively low doses of treatment, median 3 mcg/kg/d. The response is to increase the median ANC 5 fold, a response sufficient to reduce the occurrence of infections and severity of symptoms of enterocolitis. We reviewed pregnancy data for three women. These data

suggest a benefit of G-CSF to permit successful pregnancies, consistent with other reports. [24–25]

Our longitudinal observations show that patients have sustained long-term responses to G-CSF maintained on roughly the same dose of G-CSF for very long periods, i.e. >29 years. Splenomegaly is a very common feature, but the enlargement is usually gradual with low dose G-CSF, and massive enlargement of the spleen is an unexpected complication with this approach to treatment. Splenomegaly and the consequent abdominal pain, however, are the dose limiting features of G-CSF treatment. It is unclear if the symptoms of enterocolitis which improve with G-CSF would respond even better if the higher doses of G-CSF could be administered and the ANC further increased.

There are now a total of eight reported cases of acute myeloid leukemia in patients with GSD Ib, one patient from the era before the availability of G-CSF, and seven cases during the G-CSF era. All of these cases have occurred after 6 to 25 years of G-CSF treatment. MDS/AML also occurs in patients with severe congenital neutropenia who were treated with G-CSF. [26, 27] We estimate that risk is relatively low, 4 cases in this cohort prospectively followed for more than 1200 patient years. In congenital neutropenia, there is an association with G-CSF doses and there are some specific mutations that appear to carry increased risk of AML. [27] It is not yet known if certain mutations in GSD Ib convey greater risk. It is noteworthy that G-CSF is used in the treatment of a variety of other diseases associated with severe chronic neutropenia, including cyclic neutropenia, idiopathic neutropenia and autoimmune neutropenia, without a clearly recognized risk of AML. [28, 29] It is also noteworthy that patients with other form of glycogen storage diseases are not reported to have a predilection to leukemia. We interpret these data as suggesting the neutropenia in GSD Ib, as in severe congenital neutropenia and other marrow failure disorders, is primarily attributable to the intrinsic marrow defect, and that it is not directly attributable to G-CSF therapy. [30]

In summary, G-CSF has proven to be a very helpful treatment for GSD Ib patients, but treatment must be monitored carefully. Patients also should be aware that there is a risk of MDS/AML, a low risk, but a concern that cannot be overlooked in providing good advice in long term care.

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Key Points

- Neutropenia and neutrophil dysfunction are intrinsic features of glycogen storage disease Ib.
- For more than 25 years many of these patients have been treated with granulocyte colony stimulating factor (G-CSF).
- Recurrent bacterial infections and enterocolitis are common complications that are reduced, but are not eliminated, with G-CSF.
- This report summarizes the occurrence of myelodysplasia and acute myeloid leukemia in GSD Ib.

Purpose of review

Glycogen storage disease Ib is characterized by hepatomegaly, hypoglycemia, neutropenia, enterocolitis and recurrent bacterial infections. It is attributable to mutations in *G6PT1*, the gene for the glucose-6-phosphate transporter responsible for transport of glucose into the endoplasmic reticulum. Neutropenia in GSD Ib is now frequently treated with granulocyte colony-stimulating factor (G-CSF). We formed a cooperative group to review outcomes of the long term treatment of GSD Ib patients treated with G-CSF.

Recent Findings

The study enrolled 103 patients (48 males, 55 females), including 47 currently adult patients. All of these patients were treated with G-CSF, starting at a median age of 3.8 years (range 0.04 to 33.9 years) with a median dose of 3.0 mcg/kg/day (range 0.01 to 93.1 mcg/kg/day) for a median of 10.3 years (range 0.01 to 29.3 years). Neutrophils increased in response to G-CSF in all patients (median values before G-CSF $0.2 \times 10^9/L$, on G-CSF $1.20 \times 10^9/L$). Treatment increased spleen size (before G-CSF, 47%, on treatment on G-CSF 76%), and splenomegaly was the dose-limiting adverse effect of treatment (pain and early satiety). Clinical observations and records attest to reduce frequency of infectious events and the severity of inflammatory bowel symptoms, but fever and recurrent infections remain a significant problem. In the cohort of patients followed carefully through the Severe Chronic Neutropenia International Registry (SCNIR), 4 patients have developed myelodysplasia (MDS) or acute myeloid leukemia (AML) and we are aware of 4 other cases, (altogether 7 on G-CSF, 1 never treated with G-CSF). Liver transplantation in 5 patients did not correct neutropenia. Four patients had hematopoietic stem cell transplantation; 2 adults and 2 children were transplanted; 1 adult and one child survived.

Table 1

Demographics

Population	Gender		Age at Last Contact <i>median, (mean ±SEM, range)</i>	ANC Before G-CSF (N=90) <i>median, (mean ±SEM, range)</i>	Hematocrit Before G- CSF (N=84) <i>median, (mean ±SEM, range)</i>	Hemoglobin Before G- CSF (N=88) <i>median, (mean ±SEM, range)</i>	Platelets Before G- CSF (N=86) <i>median, (mean ±SEM, range)</i>
	F	M					
Children (< 18)	29	27	10.1 (10.3 ± 0.6, 0.6 – 17.6)	0.2 (1.2 ± 0.4, 0.0 – 14.7)	32.0 (33.9 ± 1.1, 23.9 – 64.2)	10.5 (11.3 ± 0.4, 7.8 – 22.6)	452 (453 ± 22, 113 – 769)
Adults (18)	26	21	26.9 (28.6 ± 1.2, 18.2 – 47.0)	0.2 (0.8 ± 0.4, 0.0 – 16.3)	32.5 (32.2 ± 0.9, 23.4 – 53.2)	10.6 (10.8 ± 0.3, 7.8 – 17.2)	478 (513 ± 32, 170 – 1071)
Total	55	48	17.2 (18.6 ± 1.1, 0.6 – 47.0)	0.2 (1.0 ± 0.3, 0.0 – 16.3)	32.1 (33.3 ± 0.7, 23.4 – 64.2)	10.6 (11.1 ± 0.3, 7.8 – 22.6)	463 (479 ± 19, 113 – 1071)

Table 2

G-CSF Treatment and Response

Population	Age at Initial G-CSF Treatment <i>median, (mean ±SEM, range)</i>		G-CSF Dose <i>median, (mean ±SEM, range)</i>		G-CSF Years of Exposure <i>median, (mean ±SEM, range)</i>		ANC After G-CSF <i>median, (mean ±SEM, range)</i>		Hematocrit After G-CSF <i>median, (mean ±SEM, range)</i>		Hemoglobin After G-CSF <i>median, (mean ±SEM, range)</i>		Platelets After G-CSF <i>median, (mean ±SEM, range)</i>	
	1.43	(3.09 ± 0.50, 0.04 – 17.18)	2.71	(3.31 ± 0.32, 0.15 – 24.57)	7.25	(7.08 ± 0.54, 0.01 – 16.36)	1.1	(2.0 ± 0.2, 0.0 – 68.5)	32.4	(32.8 ± 0.5, 15.7 – 53.8)	10.9	(10.9 ± 0.2, 5.0 – 18.4)	273	(299 ± 17, 19 – 944)
Children (< 18)	1.43	(3.09 ± 0.50, 0.04 – 17.18)	2.71	(3.31 ± 0.32, 0.15 – 24.57)	7.25	(7.08 ± 0.54, 0.01 – 16.36)	1.1	(2.0 ± 0.2, 0.0 – 68.5)	32.4	(32.8 ± 0.5, 15.7 – 53.8)	10.9	(10.9 ± 0.2, 5.0 – 18.4)	273	(299 ± 17, 19 – 944)
Adults (18)	9.09	(10.77 ± 1.30, 0.23 – 33.93)	3.03	(4.63 ± 0.67, 0.01 – 93.10)	18.13	(17.72 ± 1.05, 0.08 – 29.33)	1.4	(2.5 ± 0.3, 0.0 – 65.2)	32.3	(32.1 ± 0.5, 13.0 – 46.9)	10.7	(10.6 ± 0.2, 4.1 – 16.1)	231	(284 ± 27, 32 – 1697)
Total	3.83	(6.55 ± 0.75, 0.04 – 33.93)	3.00	(3.94 ± 0.37, 0.01 – 93.10)	10.31	(11.88 ± 0.77, 0.01 – 29.33)	1.2	(2.2 ± 0.2, 0.0 – 68.5)	32.4	(32.5 ± 0.4, 13.0 – 53.8)	10.8	(10.8 ± 0.1, 4.1 – 18.4)	258	(292 ± 15, 19 – 1697)

Table 3 –

GSD 1b Patients and Myelodysplasia or Acute Myeloid Leukemia

Patient ID Number	Year Reported	GSD Mutation	Pre G-CSF ANC Median (Range)	Age at Start of G-CSF Treatment	Years of Treatment with G-CSF	G-CSF Median Dose mcg/kg/day (Range)	Post ANC Median (Range)	Age at MDS/A ML
1	2009	Unknown	0.81 (0.27–6.83)	3.8	13.8	0.94 (0.94–1.32)	1.63 (0.01–15.8)	16.7
2	2012	Unknown	0.50 (0.11–0.74)	1.9	18.7	3.18 (1.42–7.18)	1.9 (0.59–12.1)	19.7
3	2017	Unknown	0.44 (0.25–0.85)	3.9	25	6.5 (3.21–6.5)	1.17 (0–3.13)	28.8
4	2012	1211 del CT, IVS8+1 G>A	Unknown	0.42	9.5	(2.3–4.05)	Unknown	10
5	1984	Not tested	Unknown	No G-CSF	No G-CSF	No G-CSF	No G-CSF	4
6	2002	Unknown	0.4 (0.21–0.71)	8	6	2.5 (1.7–4.6)	0.85 (0.7–0.9)	14
7	2008	1211 del CT	Unknown	14	14	2.83	Unknown	28
8	2018	Unknown	Unknown	Infancy	19	Unknown	Unknown	19

Data sources:

#1, 2, 3 Cases from SCNIR-Seattle

#3: Khalaf, et al, Submitted

#4: Case from SCNIR Hannover

#5: Simmons, et al, J Pediatr. 1984;105(3):428–31

#6: Pinsk, et al, J Pediatr Hematol Oncol. 2002;24(9):756–8

#7: Schroeder, et al, J Med Case Rep. 2008;2:319

#8: Li, et al, J Pediatr Hematol Oncol. 2018;35: 45–51