Dasiglucagon: A New Hope for Diazoxide-unresponsive, Nonfocal Congenital Hyperinsulinism?

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Abbreviations: CHI, congenital hyperinsulinism; EMA, European Medicines Agency; FDA, US Food and Drug Administration; SMPG, self-monitored plasma glucose.

Congenital hyperinsulinism (CHI) is a life-threatening condition in which pancreatic β cells secrete insulin irrespective of blood glucose concentration (1). CHI leads to precocious, persistent, and severe hypoglycemia from the neonatal period onward, potentially resulting in brain damage, which can cause permanent seizure disorders, learning disabilities, movement and vision disorders, developmental disabilities, cerebral palsy, and even death (2). Therefore, a prompt diagnosis and effective treatment are deemed mandatory.

Currently, long-term therapeutic options for CHI include nutritional support, medical therapy, and surgical intervention, although only one drug has been approved so far by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for CHI: diazoxide, an adenosine triphosphate potassium channel activator that prevents the efflux of insulin from β cells.

Not every child with CHI responds to the same treatment, and under the label "CHI" lies a heterogeneous group of disorders that we might distinguish according to (a) their responsiveness to diazoxide (40%-80%) or not, and (b) the possibility of a complete recovery after localized surgical excision if a focal lesion is identified at ^{18}F-DOPA positron emission tomography scan (24%-50%) or not. The presence of pathogenic mutations in specific genes affecting the adenosine triphosphate potassium channel itself (ie, *ABCC8/KCNJ11*) may help to predict both diazoxide unresponsiveness and focal hyperinsulinism.

Unfortunately, a considerable portion of patients do not respond to existing pharmacotherapies and are not candidates for a resolutive surgical approach, with complex disease management and a high burden on caregivers. In these children, other classes of medications—such as somatostatin analogues (octreotide and lantreotide) (3), mechanistic target of rapamycin inhibitors (sirolimus) (4), and reconstituted glucagon (5)—are used in an off-label fashion. Apart from using drugs not approved for CHI, present therapy options may be ineffective or complicated by side effects. Even the burdensome nutritional support through continuous feeding may not be sufficient. Subtotal or near-total pancreatectomy may therefore be required, but this approach may fail to avoid persistent hypoglycemia (40%-60%) or—on the other side—endocrine and exocrine pancreatic insufficiency may develop.

In this context of significant unmet medical need for more and better treatment options, a recent paper by Thornton et al (6) reported the efficacy and safety of dasiglucagon, a newer stable form of glucagon. The reconstituted glucagon —despite having demonstrated effectiveness as a glucose infusion rate sparing and as a potential preoperative stabilizing bridge therapy—is not currently approved for CHI and is not suitable for long-term use in a domestic setting. Dasiglucagon is a novel analogue of human glucagon, consisting of 29 amino acids with 7 substitutions relative to native glucagon. This modification enhances its physical and chemical stability, allowing dasiglucagon to be used in a ready-to-use aqueous solution (instead of being reconstituted) and reducing its tendency to form fibrils so that it can be used with infusion pumps. Additionally, dasiglucagon has a longer half-life of approximately 30 minutes, a delayed peak glucose concentration (35 minutes compared to 20 minutes after the administration of reconstituted glucagon), and similar adverse events to the reconstituted formulation. In March 2021, dasiglucagon was approved by the FDA as a rescue treatment for severe hypoglycemia in adults and children with diabetes aged 6 years and older (the marketing authorization application was submitted to EMA only in June 2023). Preliminary data presented at the ESPE conference in 2022 (7) suggested the potential benefit of dasiglucagon in CHI patients during the first year of age: In the first part of the study (a double-blind, placebo-controlled, 48-hour crossover study), dasiglucagon reduced by 55% the need for intravenous infusion of glucose compared to placebo, while in the second part (a 21-day, open-label extension), 10 out of 12 infants were weaned from intravenous glucose for at least 12 hours and 7 of them until the end of the trial, without having surgery.

In the recent open-label, randomized, international phase 3 trial, dasiglucagon was evaluated in a home-care setting in 32 children aged 3 months to 12 years with CHI and persistent hypoglycemia (defined as ≥3 episodes of hypoglycemia per week, based on self-monitored plasma glucose, SMPG). One-third of them had a subtotal or near-total pancreatectomy performed. Dasiglucagon was used for subcutaneous infusion via an infusion pump (10-70 µg/h) as an add-on treatment to standard of care (6).

The primary end point of the study was the rate of hypoglycemia and it was not met: Dasiglucagon treatment did not significantly reduce the number of hypoglycemic events per week; however, these events were based on SMPG, recorded on an infrequent basis (at least 3 times per day, except when hypoglycemia was clinically suspected, but time and frequency were not fixed). However, SMPG provides only snapshot information and may fail to detect hypoglycemic events that occur on an irregular basis, at unsuspected moments, especially overnight or in asymptomatic patients (8). On the contrary, continuous glucose monitoring systems—albeit still off-label—allow glucose level recognition every 5 minutes and thanks to the alarms could help decrease exposure to prolonged or severe hypoglycemia. This is why, although the main outcome parameter seems to be negative, we believe that this paper is an important contribution to the literature on CHI, since several important secondary outcome parameters, based on blinded continuous glucose monitoring, showed very meaningful positive results. Dasiglucagon treatment reduced by approximately 50% the time spent in hypoglycemia (<3.9 mmol/L [<70 mg/dL]) and in clinically significant hypoglycemia (<3.0 mmol/L [<54 mg/dL]), and it was also associated with a consistent reduction (61%) in nocturnal hypoglycemia.

Moreover, children treated with dasiglucagon decreased their carbohydrate intake by almost 150 g per week (while on the contrary children with standard of care increased their intake by >150 g/wk), the treatment was well tolerated (skin reactions and gastrointestinal disturbances were the most frequently reported adverse events), and 31 of the 32 participants continued into the long-term extension trial.

The request for approval to the FDA for dasiglucagon in the prevention and treatment of hypoglycemia in pediatric patients aged 7 days or older with CHI was submitted in June 2023, and we hope that this might open a new chapter in CHI management.

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