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Case Report

Successful Treatment of Hypoglycemia With Alpelisib in Pediatric Patients With *PIK3CA*-Related Overgrowth Spectrum

Nat Nasomyont, Meilan M. Rutter, and Philippe F. Backeljauw

Division of Endocrinology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati 45229, OH, USA

Correspondence: Nat Nasomyont, MD, MS, 3333 Burnet Avenue, MLC 7012, Cincinnati, OH 45229, USA. Email: nat.nasomyont@cchmc.org.

Abstract

Activating mutations in the *PIK3CA* gene, causing phosphoinositide 3-kinase (PI3K) hyperactivation, are rare causes of hypoglycemia. We report the novel use of alpelisib (a PI3K inhibitor) for the treatment of hypoketotic, hypoinsulinemic hypoglycemia in 2 children with *PIK3CA*-related overgrowth spectrum (PROS). Patient 1 was a 7-month-old girl who presented with a hypoglycemic seizure. Despite nutritional management including continuous feeds, she continued to have frequent hypoglycemia. At age 2.8 years, alpelisib was started at 50 mg daily and titrated to 100 mg daily. She was weaned off nocturnal continuous feeds by 8 months. She developed colitis when the alpelisib dose was increased to 125 mg, but this resolved with a dose decrease and medical management. At age 5.3 years, she was doing well with rare hypoglycemia. Her accelerated growth stabilized. Patient 2 was a 3-year-old boy who developed hypoglycemia in early infancy. Alpelisib 50 mg daily was started due to recurrent hypoglycemia despite nutritional management. He came off continuous feeds after 4 months, with decreased hypoglycemia frequency. At age 4.5 years, he had not experienced side effects from treatment. In conclusion, alpelisib appears to be effective in decreasing PROS-related hypoglycemia frequency and severity and should be considered for refractory hypoglycemia in this condition.

Key Words: alpelisib, PIK3CA, PROS, hypoglycemia, pediatrics

Abbreviations: CGM, continuous glucose monitor; FDA, U.S. Food and Drug Administration; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein-3; PI3K, phosphoinositide 3-kinase; PROS, *PIK3CA*-related overgrowth spectrum; rhGH, recombinant human GH.

Introduction

PIK3CA-related overgrowth spectrum (PROS) is a group of disorders caused by post-zygotic activating mutations in the *PIK3CA* gene, which encodes the α-subunit of phosphoinositide 3-kinase (PI3K). The activation of the PI3K/AKT/mTOR pathway results in cell growth/differentiation, glucose utilization and protein synthesis (Fig. 1). Clinical manifestations of PROS may include somatic overgrowth, vascular/lymphatic malformation, epidermal nevi, and megalencephaly, without clear genotype-phenotype correlation [1]. Hypoglycemia due to activating *PIK3CA* mutation has been increasingly recognized in patients with PROS [2-4]. Hypoglycemia presentation ranges from intermittent mild hypoglycemia not requiring treatment to severe neonatal hypoglycemia. Complex starch and/or continuous enteral feeds are commonly used, but alone may not prevent severe hypoglycemia associated with PROS.

Alpelisib is an oral agent that selectively inhibits the *PIK3CA*-dependent PI3K/AKT/mTOR pathway. The U.S. Food and Drug Administration (FDA) first approved alpelisib in combination with fulvestrant for the treatment of *PIK3CA*-mutated breast cancer. The FDA also recently approved the use of alpelisib for the management of children and adults with PROS with severe or life-threatening vascular malformations and tissue overgrowth. However, there are no reports of its use for treatment of PROS-related hypoglycemia. We describe the novel use of alpelisib for the treatment of hypoglycemia in 2 children with PROS.

Case Presentations

Patient 1 was a 7-month-old girl with symmetrical overgrowth (length +2.5 SD, weight +0.9 SD, head circumference +7.4 SD), polymicrogyria, hydrocephalus, seizures (managed with anti-epileptics), and gross motor developmental delay, who presented to our endocrinology service with a hypoglycemic seizure. Our evaluation showed nonketotic, hypoinsulinemic hypoglycemia and low growth hormone (GH), insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) concentrations (Table 1). Genetic testing revealed a c.1048G > A p.(Asp350Asn) variant in *PIK3CA*, confirming PROS. Due to frequent hypoglycemia, we started her on a schedule of frequent high-calorie meals, cornstarch-enriched bolus feeds, and continuous enteral feeds (Similac Pro-Sensitive, RCF, and Nourish) via a gastrostomy tube. Despite this, she continued to have frequent hypoglycemic episodes with glucose concentrations of <70 mg/dL (3.9 mmol/L) measured via a continuous glucose

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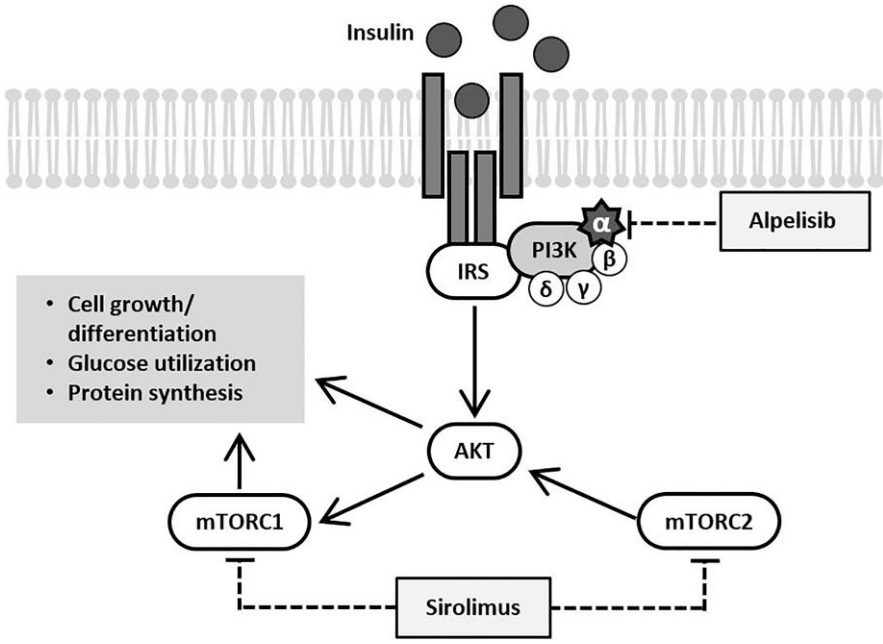

Figure 1. Schematic diagram of the PI3K/AKT/mTOR pathway downstream from the insulin receptor and available targeted pharmacologic therapies (alpelisib and sirolimus). Abbreviations: AKT, protein kinase B; IRS, insulin receptor substrate; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI3, phosphoinositide 3-kinase.

Table 1. Summary of baseline laboratory values at the diagnosis of hypoglycemia in patients 1 and 2

Laboratory values (reference range)	Patient 1	Patient 2
Glucose (65–115 mg/dL)	42	52
Insulin (<2–13 mcIU/mL)	0.8	<2
Beta-hydroxybutyrate (≤0.35 mmol/L)	0.19	0.19
Free fatty acids (≤0.99 mmol/L)	0.16	0.26
Growth hormone (≤6 ng/mL)	3.0	8.2
IGF-1 (18.6–128.1 ng/mL)	21.6	NA
IGFBP-3 (1137–3498 ng/mL)	579	NA

Abbreviations: NA, not available; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3.

monitor (CGM) 5% to 15% of the time. Trials of recombinant human (rh) GH and sirolimus therapies (for 16 and 13 months, respectively) failed to reduce hypoglycemia frequency. While her seizures abated and she was able to discontinue anti-epileptics, she remained dependent on nocturnal continuous enteral feeds (glucose requirement ± 4 mg/kg/min) and required multiple hospitalizations for feeding intolerance with hypoglycemia requiring parenteral dextrose infusion.

Patient 2 was a 3-year-old boy with PROS who presented to our endocrinology clinic for a second opinion to evaluate persistent hypoglycemia. He had polymicrogyria, macrocephaly, cutaneous capillary malformations, mild body asymmetry, global developmental delay, and primary hypothyroidism. The diagnosis of PROS had been confirmed by documenting a pathogenic *PIK3CA* variant (p.Met1043Ile). He had had hypoglycemia from birth, but this had not been persistent until age 5 months. An evaluation for hypoglycemia at that time revealed hypoketotic, hypoinsulinemic hypoglycemia (Table 1). He subsequently started full continuous enteral feeds via a gastrostomy tube and transitioned to nocturnal continuous feeds with Polycal (glucose requirement ± 3 mg/kg/min) and frequent meals to prevent recurrent hypoglycemia. A CGM showed he was hypoglycemic (<70 mg/dL or 3.9 mmol/L) 12% of the time. He required several hospitalizations for severe hypoglycemia due to feeding intolerance. His height was at −1.2 SD, weight was at +1.3 SD, and head circumference was at +9.5 SD.

Treatment and Outcome

We enrolled both patients in the Novartis Managed Access Program®, which provided access to alpelisib for patients with PROS. The treatment goal was to improve glucose homeostasis and eliminate dependency on continuous feeds. The Cincinnati Children's Hospital Medical Center Institutional Review Board reviewed and approved the treatment protocol. The patients' parents provided informed consent before treatment started.

We started Patient 1 on alpelisib 50 mg daily (a recommended pediatric dose) at age 2.9 years. After 2 months of therapy, the frequency of hypoglycemia was consistently <5%. Alpelisib was titrated (by 25 mg increments) to 100 mg daily and she discontinued nocturnal continuous after 8 months (Fig. 2A). She still required intermittent daytime bolus and cornstarch feeds because of her limited oral intake. Her accelerated height velocity decreased during the first year of therapy, and subsequently tracked along her target height percentile (Fig. 2B). Her accelerated head circumference growth stabilized. IGF-1 and IGFBP-3 normalized on therapy (57.8 ng/mL [7.55 nmol/L] and 2775 ng/mL [362.8 nmol/L], respectively). Laboratory safety indices (hemoglobin A1c, blood chemistries and lipid panel) remained normal. Following the FDA approval of alpelisib for PROS indication, she was transitioned to commercial alpelisib 125 mg

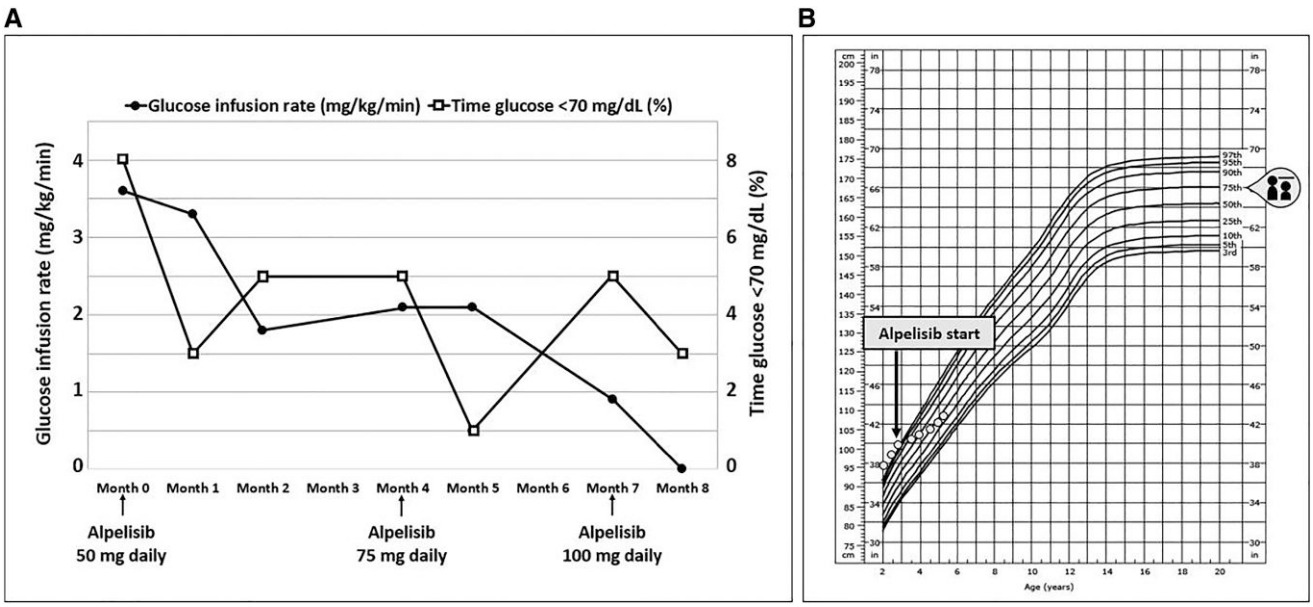

Figure 2. Overnight glucose infusion rate and hypoglycemia frequency in relation to alpelisib therapy (A) and linear growth (B) of Patient 1.

tablet daily at age 4.8 years. One month later, she developed fever, bloody diarrhea, and weight loss. Upper endoscopy and colonoscopy showed diffuse inflammation along the gastrointestinal tract with microscopic findings of granulomas, suggestive of Crohn's disease/colitis. She was treated with sulfasalazine, with rapid resolution of her symptoms. Because sulfasalazine (a Breast Cancer Resistance Protein [BCRP] inhibitor) may increase alpelisib (a BCRP substrate) concentrations and have potential drug-related adverse effects, we lowered her alpelisib dose to 50 mg daily. At age 5.3 years, she was continuing to do well on this combination therapy. Her developmental milestones were age-appropriate for language, social, and fine motor skills. She could walk unassisted with a mild gait abnormality.

We started Patient 2 on alpelisib 50 mg daily at age 3.8 years. He discontinued overnight feeds 3 months after the initiation of alpelisib. At age 4.5 years, he was continuing to do well, with diminished frequency of hypoglycemia (< 3%, as measured by CGM). He had not experienced any side effects from alpelisib. Laboratory safety indices remained normal. His height SD remained unchanged (−1.1 SD). He was receiving ongoing therapy for motor developmental delay (unable to walk without support) and language delay (using gestures and facial expressions to communicate).

Discussion

While recently recognized as a manifestation of PROS, there is no consensus regarding the screening and management of hypoglycemia in this patient population. Without routine screening, hypoglycemic episodes can go unrecognized or wrongly assumed to be epilepsy, as with Patient 1. Because severe hypoglycemia can occur in the neonatal period, routine screening with a controlled fast will help identify patients with PROS at risk for hypoglycemia and prevent its sequelae [3].

Typical long-term management of recurrent hypoglycemia in infants and young children with PROS consists of frequent carbohydrate-enriched meals and continuous enteral feeds [2, 4]. Such nutritional management may not be sufficient for normal glucose homeostasis, predisposing patients to severe hypoglycemia in the event of feeding intolerance, intercurrent illness, or feeding tube displacement. Pharmacologic therapy with diazoxide has been attempted in several patients without benefit [2]. Due to low GH concentrations observed in some patients, rhGH therapy has also been recommended. While diminished linear growth is not a common feature of PROS, Davis et al reported a small subset of patients who had diminished growth (several of whom also had hypoglycemia) and GH provocative testing indicative of GH insufficiency [5]. Although the authors observed increased height velocity with rhGH therapy, treatment effect on glucose homeostasis was not documented. While Patient 1 had low GH, IGF-1, and IGFBP-3 concentrations at the time of hypoglycemia, she did not have growth failure. Furthermore, rhGH treatment did not normalize hypoglycemia or alter her growth trajectory. In line with our experience, Stutterd et al did not observe a change in IGF-1 and IGFBP-3 concentrations or height velocity in a patient treated with rhGH [4]. It is believed that patients with PROS do not have GH deficiency, but that a low GH secretory pattern is more a reflection of hypothalamic PI3K activation, mimicking an IGF-1 effect [2]. The difference in location of the post-zygotic *PIK3CA* mutation (whether or not it occurs at the hypothalamus and pituitary gland) may explain the variability in growth pattern and response to rhGH therapy in this population [5]. Lastly, by targeting the mTOR pathway (Fig. 1), sirolimus has the potential to provide therapeutic benefit in patients with PROS [2]. A trial of sirolimus therapy showed a modest reduction of pathological tissue overgrowth [6]. However, we did not observe any improvement in hypoglycemia severity or frequency with sirolimus in Patient 1.

Alpelisib is an emerging PIK3CA inhibitor developed for oncologic conditions associated with *PIK3CA* mutations. Venot et al reported the first use of alpelisib as a treatment for children and adults with PROS [7]. In this trial, all 14 children who started on alpelisib 50 mg daily demonstrated a reduction in the size of vascular malformations after 3 to 6 months. Subsequently, clinical benefits and a reassuring

safety profile of alpelisib in a clinical study of PROS (EPIK-P1), which included 39 children aged >2 years, led to the FDA approval for this indication [8]. Because hyperglycemia is common (in 77%) in adult patients with breast cancer treated with alpelisib (300-350 mg daily) [9], we hypothesized that alpelisib would be effective in decreasing the frequency and severity of hypoglycemia in our patients. Both of our patients demonstrated decreased severity and frequency of hypoglycemia with doses of 50 and 100 mg daily; both discontinued continuous enteral feeds by 4 to 8 months of therapy. Both patients' caregivers also reported increased health-related quality of life following treatment initiation. Lastly, we observed stabilization of macrocephaly, improvement in growth pattern, and normalization of IGF-1 and IGFBP-3 concentrations in Patient 1, who had been on treatment for more than 2 years. We postulate these may be direct consequences of alpelisib targeting the dysregulation of the PI3K/AKT/mTOR pathway downstream to the insulin and IGF-1 receptors. The effects of alpelisib on linear growth and the GH-IGF-1 axis merit further investigation.

Our patients tolerated alpelisib well, although Patient 1 developed colitis on a dose of 125 mg daily. Hyperglycemia and gastrointestinal symptoms are the most common adverse effects of alpelisib. Severe hyperglycemia and diabetic ketoacidosis were reported in many adult patients with breast cancer on alpelisib therapy, with mild hyperglycemia not requiring intervention observed in a few patients (12%) with PROS [8]. It is possible that development of severe hyperglycemia is dose-dependent, as much higher doses of alpelisib are needed for cancer treatment. In keeping with the initial report [7], we observed stable hemoglobin A1c values in our patients. Regarding gastrointestinal adverse effects, only mild/grade 1 diarrhea occurred in some (16%) patients with PROS [8]. To date, only a small number of adults with breast cancer who were treated with higher doses of alpelisib have been reported with more severe gastrointestinal symptoms, including colitis, usually occurring within 6 months of treatment initiation [10]. It is unclear if the colitis symptoms in our patient were associated with the alpelisib dose increase. Given that our patient continued to do well on a lower alpelisib dose, the benefits of continuing therapy appear to outweigh its risk.

In conclusion, we report 2 pediatric patients with hypoglycemia associated with activating *PIK3CA* mutations, who were successfully managed with a novel and promising PI3K inhibitor therapeutic approach. We recommend that, for PROS patients with recurrent hypoglycemia refractory to continuous enteral feeds and other treatment modalities, targeted therapy with alpelisib should be instituted. Additional experience with this approach for correcting hypoglycemia in patients with PROS is needed in order to consider it as first-line therapy.

Learning Points

- Hypoinsulinemic hypoglycemia is a reported feature of PIK3CA-related overgrowth spectrum (PROS) and is often refractory to nutritional management.
- Alpelisib is a PI3K inhibitor indicated for the management of severe vascular malformation and overgrowth associated with PROS, but it has not been reported for treatment of hypoglycemia.
- Targeted therapy with alpelisib appears to decrease hypoglycemia severity and frequency in pediatric patients with PROS.

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Contributors

All authors made individual contributions to authorship. N.N., M.R. and P.B. were involved in the diagnosis and management of patients and manuscript submission. All authors reviewed and approved the final draft.

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Disclosures

The authors have no conflicts of interest to disclose.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patients' guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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