JPPT | Review

Alpelisib: A Novel Agent for PIK3CA-Related Overgrowth Spectrum

Katarina Nadjkovic, PharmD and Kevin Lonabaugh, PharmD

The aim of this review is to present the information a clinician will need when considering alpelisib therapy for a patient diagnosed with PIK3CA-related overgrowth spectrum (PROS). PROS is a condition caused by a somatic recessive gain-of-function mutation in the gene encoding phosphatidylinositol-3-kinase (PI3K). PROS is rare, affecting approximately 14 births per 1 million. PROS affects many different tissues including skin, bone, vascular, adipose, and connective tissues, thus its presentations vary widely. The presentation of PROS is often described as mosaic, as the disease typically does not affect all cells in the body. For patients two years of age and older requiring systemic therapy, alpelisib is an option which was recently granted accelerated approval by the US Food and Drug Administration (FDA) on April 5, 2022. Alpelisib is an inhibitor of PI3K, slowing the progression of existing lesions and preventing new lesions in patients with PROS. Important drug interactions exist with both CYP3A4 inducers and CYP2C9 substrates. Additionally, providers of patients receiving alpelisib should be aware of potential side effects including hypersensitivity, severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea, and embryo-fetal toxicity. Despite the potential for adverse events, alpelisib has provided clinical benefit to many patients with PROS as evidenced by the current literature. This review collects and summarizes the currently available evidence, including a recently published case series and multiple case reports. Alpelisib is a promising new option for patients with PROS.

ABBREVIATIONS AUC,area under curve; BCRP, breast cancer resistance protein; CLOVES, Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/skeletal/spinal anomalies; C_{max}, maximum concentration; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; DRESS, drug rash with eosinophilia and systemic symptoms; EM, erythema multiforme; FDA, US Food and Drug Administration; GLA, Generalized Lymphatic Anomaly; KTS, Klippel-Trénaunay syndrome; LIC, Vascular Malformations with Low-Grade Intravascular Coagulopathy; PI3K, phosphatidylinositol-3-kinase; PIK3CA, phosphatidylinositol-3-kinase catalytic subunit α; PROS, PIK3CA-related overgrowth spectrum; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

KEYWORDS Alpelisib; BYL719; CLOVES; PROS

J Pediatr Pharmacol Ther 2023;28(7):590–594

DOI: 10.5863/1551-6776-28.7.590

Introduction

PIK3CA-related overgrowth spectrum (PROS) is an umbrella term for medical conditions caused by a somatic mutation in PIK3CA. PROS is a rare condition, affecting approximately 14 births per 1 million.[1] Medical conditions which fall under the term PROS include but are not limited to Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/skeletal/spinal anomalies (CLOVES) syndrome, Klippel-Trénaunay syndrome (KTS), Generalized Lymphatic Anomaly (GLA), and sometimes Vascular Malformations with Low-Grade Intravascular Coagulopathy (LIC) depending on the mutation present. Due to the rarity of these mutations, the true incidence of many of the specific subtypes of PROS is unknown. Common presentations of PROS include enlarged digits, scoliosis, abnormal growth of certain body parts including entire limbs, vascular malformations such as port-wine stains and varicose veins, and lymphatic malformations. PROS carries significant complications, including benign and malignant tumors, bone and soft tissue deformations, disfigurement, functional disability, spinal and neurological issues, coagulopathies including bleeding and thrombosis, recurrent soft tissue infections, acute and chronic pain, and death. Even people with the same condition may have differences in the manifestation, symptoms, and severity of the disease.[2]

Currently, the management of PROS is limited and may be based on symptomatic management rather than the PIK3CA mutation causing the disease state. Non-pharmacologic interventions such as compression garments and lymphatic massages may reduce peripheral

and lymphatic edema. Surgical intervention is used for debulking and addressing extremity length discrepancies. However, when systemic pharmacotherapy is required, options are limited. For vascular and lymphatic anomalies in which the offending genetic mutation is unknown or targeted therapy does not exist, sirolimus may be used. Sirolimus works downstream of alpelisib as an inhibitor of the mammalian target of rapamycin (mTOR) in order to stop cellular proliferation. Though sirolimus still plays a role in treating PROS, alpelisib has quickly become the drug of choice for medical management of PROS thanks to its targeted mechanism of action earlier on in the cellular proliferation pathway.[2]

Mechanism of Action

Alpelisib is a PI3K inhibitor approved by the FDA under the brand name Vijoice (Novartis Pharmaceuticals; East Hanover, NJ) for adult and pediatric patients at least 2 years old with PROS requiring systemic therapy.[3] Prior to approval for treatment of PROS, alpelisib—branded as Piqray (Novartis Pharmaceuticals; East Hanover, NJ)—was indicated for postmenopausal women and men with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer at a dose of 300 mg daily.[4] At that time, alpelisib was only used off-label for the medical management of PROS through a compassionate use managed access program.[5]

In patients with PROS, gain-of-function mutations are seen in the PI3K α catalytic subunit, PIK3CA. Such mutations can lead to bone and soft tissue malformations as well as tumor formation. Because of this, alpelisib is used to inhibit the mutated protein to reduce or limit manifestations of the disease.[2]

Pharmacokinetics/Pharmacodynamics

Due to the unique conditions giving rise to alpelisib being indicated for PROS, the pharmacodynamics and pharmacokinetics of alpelisib have not yet been studied in pediatric patients. The pharmacodynamic and pharmacokinetic data provided in the package insert are from adult patients with breast cancer using alpelisib as part of their chemotherapy regimen.

In adult oncology patients, C_{max} and AUC increase proportionally with the dose over a range of 30 mg to 450 mg daily. Absorption is increased with food intake. Taking alpelisib with a low-fat low-calorie meal (334 calories with 8.7 g of fat) increased AUC by 77% and C_{max} by 145% while a high-fat high-calorie meal (985 calories with 58.1 g of fat) increased AUC by 73% and C_{max} by 84%. These impacts of meal type on pharmacokinetics are not proposed to be clinically relevant, thus it is simply recommended that alpelisib be administered with some type of food. Under fed conditions, clearance of alpelisib is 9.2 L/hr. T_{max} occurs at 2 to 4 hours. Alpelisib has a volume of distribution of 114 L and the plasma protein binding is 89%, independent of concentration. Predicted biological half-life of alpelisib is 8 to 9 hours. Under fasted conditions, a single oral dose of 400 mg alpelisib is primarily excreted in the feces (81% of total, with 36% unchanged) and urine (14% of total with 2% unchanged).

Pharmacokinetic parameters in adults did not differ significantly based on age, sex, ethnicity, weight, mild to moderate renal impairment (CrCl 30–90 mL/min as calculated with Cockcroft-Gault formula), or mild to severe hepatic impairment (Child-Pugh Classes A, B, and C). The effect of severe renal impairment (CrCl < 30 mL/min) on the pharmacokinetics of alpelisib is unknown.[3] In adult oncology patients, alpelisib did not prolong the QT interval to a clinically relevant extent.[3,4]

Clinical Trials

Alpelisib was approved by the FDA for adult and pediatric patients over the age of 2 with PROS based on an observational retrospective chart review of patients receiving alpelisib through a compassionate use managed access program. The review, also called EPIK-P1, included 59 patients living in Australia, France, Ireland, Spain, and the United States. A detailed report of the outcomes of EPIK-P1 has not been published to date, however, the data from this retrospective chart review are available in the package insert and provide insight on the safety and efficacy of alpelisib when used to treat PROS. The primary outcome reported was the proportion of patients with response to therapy at week 24. Response to therapy for patients enrolled in EPIK-P1 was defined as: 1) at least a 20% reduction by volume of at least 1 lesion, 2) without an increase of 20% or more by volume of any 1 lesion, and 3) no new lesions. Volume was calculated upon clinician review of imaging. The manufacturer of alpelisib reports that any reduction in lesions was experienced by 74% of participants and response per the described criteria was achieved in 27% of patients, as confirmed by blinded independent central review. Seventy percent of responding patients had maintained response at 6 months and 60% had maintained response at 12 months.[5]

We searched for relevant primary literature by using the search "((PROS) OR (CLOVES) OR (KTS) OR (GLA) OR (LIC)) AND ((ALPELISIB) OR (BYL719))" on PubMed. Currently 1 case series and several case reports are published describing the use of alpelisib to treat PROS in the pediatric population.

In a case series described by Venot et al,[6] the first patient to receive alpelisib for PROS through a compassionate use program was a 29-year-old man who had undergone numerous debulking surgeries over the course of his life and developed paraplegia by the age of 20 due to spinal cord compression from a lesion mass. He had also developed severe heart failure and renal dysfunction, saw no clinical benefit from sirolimus, and was eventually transitioned from interventional

treatment to palliative care with a life expectancy of only a few months. The patient started alpelisib at a dose of 250 mg once daily. Over the following 18 months, he lost 25 kilograms in edema and lesion volume, saw a 60% reduction in volume of the lesion compressing his spinal cord, his thoracic circumference was reduced by 25%, his abdominal circumference was reduced by 39%, his heart size reduced by 25%, and his renal function increased from 33 mL/min to 52 mL/min.[6]

The second patient to receive alpelisib through a compassionate use program was a 9-year-old girl diagnosed with PROS complicated by scoliosis and lymphangioma with renal and gastrointestinal involvement. The patient started alpelisib at a dose of 50 mg once daily. She experienced a reduction in volume of all lesions and specifically showed a 40%, 54%, and 71% reduction in intra-abdominal tumor volume at 4, 6, and 12 months of treatment with alpelisib, respectively. Remarkably, her scoliosis reversed by month six of treatment with no other interventions in addition to alpelisib. Following these initial 2 case reports, the same investigators proceeded with a case series of 17 additional patients—14 children and 3 adults—all whom exhibited a positive response with minimal adverse effects attributed to alpelisib.[6]

In the months and years following this case series, many more patients have started alpelisib for the treatment of their PROS and have demonstrated similar positive clinical outcomes. Pagliazzi et al[7] reported the case of an 8-year-old girl with CLOVES syndrome, a large thoracic lymphangioma, and scoliosis who had to discontinue treatment with sirolimus after no clinical improvement and development of *Mycoplasma pneumoniae* infection at 10 months of treatment. The patient then started taking alpelisib 50 mg daily and showed promising MRI changes and no adverse effects after 1 year of treatment. Although the objective mass of the patient's lesions proved difficult to track, the researchers reported noticeable improvement in posture, lower extremity length discrepancy, and volume of lipomas. Additionally, the patients D-dimer values, which had been previously elevated prior to treatment, fell within normal limits. Garetta Fontelles et al[8] reported the case of a 2-year-old boy with CLOVES syndrome who did not previously experience adequate response with a 12-month sirolimus trial. The boy then began to receive alpelisib therapy at a dose of 50 mg daily and exhibited clinical improvement, including reduction in lesion volume. The researchers reported a 31% reduction in cystic lymphangioma mass within just a few months of treatment with alpelisib and no treatment-related adverse effects.[8]

Clinical Application

Dosing. Alpelisib is supplied as tablets in 28-day blister packs at 50 mg daily, 125 mg daily, and 250 mg daily (as 50 mg and 200 mg tablets included in the same blister pack). Dosing is based on age (Table 1). The manufacturer does not make any specific recommendations regarding dose adjustments for baseline renal or hepatic impairment. The tablets should be taken by mouth with food at the same time every day. If a dose is missed, it can be taken within 9 hours of its scheduled time. If this window has been missed, it is recommended that patients skip the missed dose and restart their regular dosing schedule the next day. If a patient vomits at any time after taking alpelisib, they should be advised to not take another dose and restart their regular dosing schedule the next day. The prescribing information for alpelisib advises patients that tablets should be taken whole and not split or chewed, however there are also instructions on how to make an oral suspension using alpelisib tablets and water for patients who have difficulty swallowing tablets. If an oral suspension is indicated, the patient should place their dose into a glass with 2 to 4 ounces of water, let stand for approximately 5 minutes, crush the tablets in the glass of water with a spoon, and stir until an oral suspension is obtained. The dose should be administered immediately after preparation. If the oral suspension is not administered within 60 minutes of preparation, it should instead be discarded. To ensure that the entire dose is received, 2 to 3 tablespoons of water should be added to the glass and stirred with the same spoon to re-suspend any remaining particles. This suspension should be immediately administered. This rinsing process may be repeated until the entire dose has been administered.[3]

Warnings and Precautions. Some warnings in the prescribing information for alpelisib are included due to the presence of these adverse effects in patients using alpelisib in the context of breast cancer. These adverse effects include severe hypersensitivity, severe cutaneous adverse reactions, and pneumonitis. Due to embryo-fetal toxicity findings in animal studies,

Table 1. Dosing Recommendations for Alpelisib Based on Age of Patient and Time on Therapy[3]

Age	Initial Dose	When to Increase	Target Dose
2–5 yr	50 mg daily	Increased dose not recommended	50 mg daily
6–17 yr	50 mg daily	After 24 wk of treatment until clinical improvement as tolerated	125 mg daily
>18 yr	250 mg daily	Upon reaching 18 years old	250 mg daily

Table 2. Rates of Hyperglycemia in Alpelisib Trials Stratified by Indication and CTCAE Grade[3,4]*

	Age of Participants in yr, Mean (Range)	Total Incidence of Hyperglycemia	Grade 1 and 2 Hyperglycemia	Grade 3 Hyperglycemia	Grade 4 Hyperglycemia
EPIK-P1 Trial *For PROS*	14 (2–38)	12%	12%	0%	0%
SOLAR-1 Trial *For breast cancer*	63 (25–92)	65%	32%	29%	4%

CTCAE, Common Terminology Criteria for Adverse Events

* CTCAE hyperglycemia grades: Grade 1 hyperglycemia is an abnormally high glucose above baseline with no indicated medical intervention. Grade 2 hyperglycemia occurs when a diabetic patient's daily management must change from baseline or an oral antiglycemic agent is initiated. Grade 3 hyperglycemia occurs when insulin therapy is initiated or hospitalized is indicated as a result of hyperglycemia. Grade 4 hyperglycemia is a life-threatening event with urgent or emergent intervention necessary. Grade 5 hyperglycemia is death.

Table 3. Dosage Adjustment Recommendations for Alpelisib Based on CTCAE Grade of Other Adverse Events (Excluding Rash and Severe Cutaneous Adverse Reactions, Hyperglycemia, Pneumonitis, Diarrhea or Colitis, and Pancreatitis)[3]*

CTCAE Grade	Recommended dose adjustment
Grade 1	No dose adjustment recommended
Grade 2	No dose adjustment recommended
Grade 3	Hold alpelisib until adverse event is grade 1 or lower. Adult patients: Continue at next lowest dose Pediatric patients: Continue at 50 mg daily or permanently discontinue alpelisib
Grade 4	Permanently discontinue alpelisib

CTCAE, Common Terminology Criteria for Adverse Events

* For detailed guidance on management of rash and severe cutaneous adverse reactions, hyperglycemia, pneumonitis, diarrhea or colitis, and pancreatitis, consult the package insert.[3]

female patients taking alpelisib who are of reproductive potential should be advised to use effective contraception while taking alpelisib and for 1 week after the last dose taken. Similarly, male patients with female partners who are of reproductive potential should use condoms while taking alpelisib and for 1 week after the last dose was taken. The prescribing information for alpelisib also contains a warning for hyperglycemia. Although this adverse event was seen both in patients taking alpelisib for breast cancer and patients taking alpelisib for PROS, the incidence and severity of hyperglycemia experienced by patients taking alpelisib for PROS was much less severe (Table 2).[3,4]

Dosage Modifications for Adverse Events. Providers should be aware of specific recommendations for select adverse events which may happen with alpelisib: hyperglycemia, pneumonitis, diarrhea, pancreatitis, and severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM), and drug rash with eosinophilia and systemic symptoms (DRESS). Detailed guidance for each of these events can be found in the package insert. For all other adverse events, the manufacturer broadly recommends adjusting the dose based on the Common Terminology Criteria for Adverse Events (CTCAE) grade severity of the adverse event (Table 3).[3] This information will be useful to practitioners as they monitor the safe use of alpelisib in the pediatric population and make appropriate dose adjustments.

Drug-Drug Interactions. Alpelisib should not be administered with strong CYP3A4 inducers. Because alpelisib is metabolized by CYP3A4, co-administration with a strong CYP3A4 inducer may significantly decrease alpelisib concentrations and exposure, decreasing its efficacy.[3] Breast cancer resistance protein (BCRP) inhibitors should be avoided in patients taking alpelisib for PROS when possible. If BCRP inhibitor therapy is necessary for another condition, adverse effects of both agents should be closely monitored. Because alpelisib is both a substrate and a modest inhibitor of BCRP, alpelisib and a co-administered BCRP inhibitor may increase the concentrations and exposure of each other, increasing the risk of adverse effects for both agents.[3] Agents sensitive to CYP2C9 induction should be closely monitored when coadministered with alpelisib. Alpelisib is a CYP2C9 inducer, so co-administration of alpelisib and a CYP2C9

substrate may decrease concentrations and exposure to the CYP2C9 substrate.[3]

Acid reducers did not significantly impact the observed pharmacokinetics of alpelisib.[3] Of note, ranitidine use decreases alpelisib AUC and C_{max}, but ranitidine has not been available since the 2020 recall.

Cost, Coverage, and Financial Assistance Options. At an average wholesale price of $39,500 per 28 day supply, alpelisib would not be a feasible option for many patients and their families without financial assistance. Fortunately, there are support services available. The manufacturer of alpelisib offers a Vijoice VIP Program for care coordination,[9] Patient Assistance Now Oncology (PANO) program for access coordination including free trials,[10] and a universal co-pay assistance program for which patients taking alpelisib can be eligible.[11]

Discussion

Alpelisib is a newly FDA-approved treatment for PROS which offers lesion reduction and prevention in a once-daily oral formulation. Before being granted accelerated approval for PROS on April 5, 2022, alpelisib was indicated for postmenopausal women and men with HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. During that time, alpelisib was prescribed and distributed for PROS off-label through compassionate use managed access programs. EPIK-P1, a retrospective chart review of these patients conducted by the manufacturer of PROS, provided evidence for accelerated approval of alpelisib for PROS. Continued approval of alpelisib for PROS relies on post-marketing safety and efficacy data.

While there are severe side effects and important warnings which providers should be aware of, alpelisib has offered effective medical management with minimal side effects for many patients with PROS requiring systemic therapy. In particular, there are some key differences in both the incidence and severity of hyperglycemia associated with alpelisib when used to treat breast cancer versus when used to treat PROS (Table 2). It would be reasonable to attribute the differences in adverse effect profiles for alpelisib in different settings to some combination of the following factors: a dramatic difference in age of patients due to different indications, low enrollment in the EPIK-P1 trial due to the rarity of PROS, and lower drug exposure with alpelisib regimens for PROS.[3,4] Overall, the evidence available in the literature is overwhelmingly positive regarding the use of alpelisib to treat PROS.[5–8]

Article Information

Affiliations. Department of Pharmacy (KRN), Sentara Martha Jefferson Hospital, Charlottesville, VA; Department of Pharmacy (KPL), University of Virginia Health System, Charlottesville, VA; School of Pharmacy (KRN), Virginia Commonwealth University, Richmond, VA.

Correspondence. Kevin Patrick Lonabaugh, PharmD; kevinpatrick@virginia.edu

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Acknowledgment. KN (BSc) was an intern at the University of Virginia Hospitals at the time of preparing and completing this manuscript.

Submitted. September 23, 2022

Accepted. January 27, 2023

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