Repurposing alpelisib, an anti-cancer drug, for the treatment of severe TIE2-mutated venous malformations: Preliminary pharmacokinetics and pharmacodynamic data

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Abstract
Extensive venous malformations involving limbs severely impact quality of life, mostly due to chronic pain and functional limitations. But patients can also display coagulopathy with associated risks of life-threatening thromboembolism and bleeding. Available pharmacological treatments (e.g., sirolimus) are not universally effective. Novel therapies are urgently needed for patients with treatment-resistant venous malformations. We report three patients with TIE-2 receptor mutations treated with alpelisib for 6 months (daily dosing: 50 mg for children weighing <50 kg and 100 mg for those >50 kg). Pain was controlled, gait improved, size of the abnormal venous network decreased, and coagulopathy dramatically improved. Drug exposure was highly variable, suggesting alpelisib dosing should be individualized to patient’s characteristics and guided by therapeutic drug monitoring.

KEYWORDS
alpelisib, pediatrics, pharmacokinetics, TIE-2 receptor, vascular anomaly, venous malformation

ABBREVIATIONS: AUC, Area under the curve; DOAC, Direct-Acting Oral Anticoagulants; HPLC, High Performance Liquid Chromatography; LIC, localized intravascular coagulopathy; LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; PK, Pharmacokinetics; VM, Venous malformation.
1 | INTRODUCTION

Extensive venous malformations (VM) involving limbs lead to chronic pain, functional impairment, and localized intravascular coagulopathy (LIC) with an associated risk of life-threatening thromboembolism and bleeding. Over 70% of sporadic VM are attributed to somatic activating mutations in the TEK gene, encoding the receptor tyrosine kinase TIE2 expressed by venous endothelial cells, leading to overactivation of the PI3K/AKT/mTOR pathway in the affected body part and aberrant venous network reshaping1-4 (Figure 1). Front-line treatment to control pain and thrombotic complications is anticoagulation (low molecular weight heparin or direct-acting oral anticoagulants)5 that improves symptoms without treating the underlying disease.

Sirolimus, a mTOR inhibitor, is used for extensive and symptomatic VM, but 10% of patients are resistant.6 In vitro studies showed superiority of alpelisib (a PIK3CA inhibitor)7 over sirolimus in inhibiting the TIE2 signaling pathway to block the effect of the mutation on vein reshaping2,8 (Figure 1).

Here, we report for the first time the use of alpelisib in patients with TIE2-mutated VMs, including outcomes and drug pharmacokinetic (PK) parameters.

2 | METHODS

2.1 | Inclusion criteria

Inclusion criteria were as follows: symptomatic VM with resistance, partial response, or contraindication to sirolimus.

2.2 | Study drug and concomitant treatment

Alpelisib (BYL719; Piqray) was obtained through Novartis’s compassionate drug access program (Managed Access Program).9 Initial daily oral doses were 50 mg for patients weighing <50 kg and 100 mg for patients weighing >50 kg. The 100 mg dose was chosen instead of the empiric fixed pediatric dosing of 50 mg to promote drug response in patients with adult weight. It was considered safe because the lowest daily dose in adults with cancer is 250 mg.10 In previously sirolimus-treated patients, sirolimus was discontinued a week prior to alpelisib start, and enoxaparin was started concomitantly to prevent thrombotic complications with sirolimus discontinuation. Enoxaparin was progressively weaned over months based on symptomatology and coagulation studies.

2.3 | Evaluation of drug response and PK

VM extent was documented by magnetic resonance imaging (MRI) and medical photography before and 6 months after alpelisib start. Bloodwork was performed prior to the initiation of alpelisib and enoxaparin and at least monthly thereafter (complete blood count with differential, lipase, glucose and glycosylated hemoglobin, liver profile including gamma-glutamyl transferase, urea, creatinine, and coagulation profile). Electrocardiography, cardiac echography, and lung function tests were obtained prior and after 6 months of treatment. Area under the curve (AUC) was obtained at 6 months (timing of blood levels: before alpelisib and 0.5, 1, 1.5, 2, 3, 6, and 8 h after). Alpelisib blood concentrations were determined with high-performance liquid chromatography (HPLC) as previously reported.11 Good specificity, linearity, accuracy, and precision were demonstrated (limit of detection: 0.97 ng/ml; limit of quantitation: 1.95 ng/ml). PK parameters were determined with noncompartmental analysis (Phoenix version 8.1.0.3530, Certara, USA).

2.4 | Adverse events

All adverse events were recorded at each clinic visit and reported as per the Sponsor and Health Canada requirements.

2.5 | Ethics

The compassionate use was approved by the Institutional Review Board. All patients provided informed consent.
3 RESULTS AND DISCUSSION

3.1 Patient phenotypes

We sent tissue biopsies from the affected body parts for a targeted next-generation sequencing panel including 25 genes involved in vascular anomalies. The panel identified the somatic TEK p.L914F mutation in all three of our patients and was negative for the remaining 24 genes including PIK3CA.

**Patient 1:** A 16-year-old female (60 kg) has an extensive leg VM infiltrating skin, subcutaneous tissues, muscles and joints with profound LIC (Figure 2). She is wheel-chair dependent due to limited lower limb function (due to equinus deformity, genu flexum, and pain) and suffers constant pain interfering with sleep and daily activities. She presented with life-threatening bleeding after a minor hymenal septum surgery, with new onset disseminated coagulopathy and was admitted to the PICU and treated with multiple blood products and heparin infusion. The bleeding stopped after 2 weeks. Her VM was sirolimus resistant12 (6-month course; trough levels: 10–15 ng/ml; induced hypertriglyceridemia).

**Patient 2:** A 12-year-old male (43 kg) displays an extensive VM of both legs, thorax, and right arm (with compression garment of the right arm) with profound LIC and history of extensive left leg thrombosis. He partially responded to sirolimus with LIC improvement (Figure 2) but with no radiological response and progressive equinus deformity despite prior surgical Achille tendon lengthening surgery (3 years course; trough levels: 8–12 ng/ml; induced chronic proteinuria13 and hypercholesterolemia).

**Patient 3:** An 18-year-old male (92 kg) has an extensive leg VM with chronic pain that started at the age of 8 and progressively restricted his activity tolerance to 5 min. Debulking surgeries and a 6-month course of enoxaparin did not improve his symptoms. Compression garment only partially alleviated associated discomfort. Also, equinus deformity reappeared after Achille tendon lengthening surgery. IgA glomerulonephritis contraindicated sirolimus.

3.2 Treatment response

**Pain** (concerns patients 1 and 3)

After a month of treatment, patient 1 was able to stop all analgesics and showed improved mobility. Pain control persisted while prophylactic subcutaneous heparin was weaned and stopped after 7 months of treatment with alpelisib. Patient 3’s walking capacity increased from 5 min to unlimited distance after 3 months, and he recovered normal daily functioning, but pain persisted unchanged when standing still.

3.3 Coagulopathy

Coagulation studies showed dramatic improvements (Figure 2). Note that D-dimer remained higher than 2 μg/ml (threshold of quantification by our laboratory) in all patients except patient 3.

3.4 General appearance and joint mobility

In the only patient with visible cutaneous involvement of the leg (patient 1), appearance improved with decreasing size of the varicosity (Figure 2). Arm compressive garments for patient 2 were downsized. Joint mobility did not significantly improve in any patient.
FIGURE 3  Pharmacokinetics of alpelisib in the study population and lipid profile: (A) 24 h concentration–time profile. (B) PK parameters of alpelisib. (C) Lipid profile on sirolimus and later alpelisib. AUC: area under the curve; VD: volume of distribution. *The last point of the AUC (at 24 h) is derived from the concentration before alpelisib administration (t₀). The AUC of patient 2 is slightly underestimated (around 15%) because the previous alpelisib administration was at 37 h (instead of 24 h) before alpelisib administration for AUC determination.

3.5  MRI imaging
The size of the VM showed a dramatic decrease in patient 1 (Figure 2) but remained relatively similar in the other patients. Venous lakes decreased in size in all treated patients (15%–72% volume decrease).

3.6  Drug exposure
AUC and other PK parameters showed high interindividual variability (Figure 3).

3.7  Safety and adverse events
Adverse events associated to alpelisib treatment included an episode of self-resolved headache with normal cerebral computed tomography scan (patient 3), two episodes of superficial thrombophlebitis, likely related to underlying disease (patients 1 and 3), and spontaneously resolved sole pain (patient 2). Sirolimus-induced dyslipidemia resolved after sirolimus discontinuation (Figure 3C). Patient 2 showed positive proteinuria during the last 6 months of sirolimus treatment (0.25 g/L; urine protein/creatinine ratio undetermined) with preserved renal function that resolved after discontinuation.

We describe for the first time the use of alpelisib in TIE2-mutated severe VM. Alpelisib is approved for PIK3CA-mutated breast cancer and for PIK3CA-related overgrowth spectrum (PROS) since April 2022. Efficacy in PIK3CA-mutated lymphatic malformations has also been demonstrated. Our study is the first to report clinical efficacy in non-PIK3CA-mutated lesions. Pain, motor function, and coagulopathy greatly improved within weeks, but tendinous retractions persisted. As pain was controlled, joint mobility became the only determinant of functionality. Serial casting and surgery will still be required to treat tendon shortening that occurred previously due to prior pain and/or because of the infiltration of muscles and tendons by the VM. Whether initiating alpelisib prior to joint retraction could prevent this complication remains to be determined.

The clinical VM improvement on alpelisib of sirolimus partial responder or nonresponder is in line with the in vitro data in TIE2-mutated VM showing superiority of alpelisib over sirolimus. Prospective comparative efficacy and safety studies are needed to determine the best first-line treatment. Unlike heparin and surgery, alpelisib is a disease-modifying drug rather than a symptomatic treatment, but prolonged or even life-long treatment may likely be required...
to suppress the effect of TIE-2 receptor overactivation. The economic implications of life-long treatment with this expensive drug cannot be overlooked.

All patients had a TEK p.L914F-mutation that strongly activates the PIK3 pathway.\textsuperscript{2,8} The effectiveness of alpelisib with less activating TEK mutations will need to be determined.

Some sparse PK data in two infants with PROS have previously been reported (trough level and 3 h after dose).\textsuperscript{16} We present the first AUC and primary PK parameters in children. Currently, alpelisib dosing in pediatrics is based on a fixed-dosing strategy irrespective of weight and age (2–18 years old: 50 mg daily oral dose).\textsuperscript{10,15} As weight represents the main determinant of drug exposure in children,\textsuperscript{17} weight-adjusted dosing was chosen. Very variable drug exposure between patients was noted despite relatively similar weight-adjusted dosing (1.1–1.7 mg/kg) (Figure 3). AUC in patient 1 was 2.6–4 times higher than in patients 3 and 2, respectively, potentially explaining her striking radiological response. Dose increase in patients 2 and 3 may improve response. Therapeutic drug monitoring may become a vital tool to tailor drug dosing to the desired systemic exposures.

Alpelisib was well tolerated. Moreover, the adverse effects noted while on sirolimus resolved after sirolimus discontinuation. Exposure to higher doses of alpelisib is unlikely to induce significant toxicity as the AUC on maximal tolerated dose in adults with cancer are significantly higher than in our patients (39,500 ng·h/ml (range: 5210–81,700 ng·h/ml); 350–400 mg daily).\textsuperscript{7,18,19} A dose-finding study is currently underway in PROS (EPIK-P2).\textsuperscript{20,21} Similar study should be performed in VM.

Despite the limited number of treated patients hindering definitive conclusions on efficacy and safety, our data suggest that alpelisib is effective in TIE2-mutated VM. Instead of a fixed dose for all children, dosing needs to be individualized to patient’s characteristics and guided by plasma drug exposure.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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