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

Niina Kleiber (kleiber.niina@gmail.com)
Centre Hospitalier Universitaire Sainte-Justine
Amandine Remy
Centre Hospitalier Universitaire Sainte-Justine
Thai Hoa Tran
Centre Hospitalier Universitaire Sainte-Justine
Josée Dubois
Centre Hospitalier Universitaire Sainte-Justine
Chantal Lapointe
Centre Hospitalier Universitaire Sainte-Justine
Paul Gavra
Centre Hospitalier Universitaire Sainte-Justine
Facundo Garcia-Bournissen
London Health Sciences Centre
Yves Théorêt
Centre Hospitalier Universitaire Sainte-Justine
Rochelle Winikoff
Centre Hospitalier Universitaire Sainte-Justine

Short Report

Keywords: personalized medicine, venous malformation, coagulopathy, alpelisib, targeted treatment, pediatrics, vascular anomaly, vascular biology

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1440565/v1

Abstract

Extensive venous malformations (VM) involving limbs severely impact quality of life, mostly due to chronic pain and functional limitations. Patients can also display coagulopathy with associated risks of life-threatening thromboembolism and bleeding. Current pharmacological VM treatments (e.g. sirolimus) are not universally effective as 10% of patients present intractable debilitating and/or critical disease. Novel therapies are therefore highly needed for treatment-resistant VM. Over 70% of sporadic VM are attributed to activating mutations in the *TEK* gene, encoding the receptor tyrosine kinase TIE2 expressed by venous endothelial cells. Despite in vitro studies showing the superiority of alpelisib over sirolimus in inhibiting TIE2 signalling pathway and vein remodelling, there are currently no clinical reports of alpelisib use in VM. Our aim was therefore to assess the effect of alpelisib in TIE-2 mutated VM and to assess its pharmacokinetics.

Three patients with a VM harboring the *TEK* L914F mutations were treated with alpelisib in an open-label compassionate use study. All patients experienced significant improvement. Pain was controlled, gait improved, size of the abnormal venous network decreased, and coagulopathy showed dramatic improvement. Drug exposure was highly variable despite similar weight-adjusted doses, suggesting that alpelisib dosing should be individualized to patient's characteristics and guided by therapeutic drug monitoring to improve clinical response.

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 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 and aberrant venous network reshaping(1–3).

Indeed, this activating mutation leads to ligand-independent phosphorylation that confers a vascular growth advantage by decreasing endothelial cell death rate(2) and induces vessel migration in aberrant directions due to loss in front-rear polarity(3). Dysregulation of angiogenic factors alters vascular development and cell migration(2). Blood stasis and altered endothelium promotes clotting and coagulopathy(1, 2, 4).

There is currently no approved treatment(5, 6). Sirolimus, a mTOR inhibitor, is the standard treatment for symptomatic VM but 10% of patients are resistant(7). Novel therapies are therefore highly needed.

In vitro studies on mutant human umbilical vein endothelial cells show that the *TEK* p.L914F mutation strongly dysregulates the AKT/PI3K/mTOR pathway(2, 8), similar to what is observed in *PIK3CA*-mutated VM(1). Interestingly, *in vitro* studies show superiority of alpelisib over sirolimus to negate the effect of the TIE-2 mutation and reshape the veins(2, 8).

Overall, these data suggest that alpelisib may be effective in case of resistance or partial response to sirolimus. Despite the rationale behind alpelisib use in VM, there is no report of its use in human.

Our aim was to assess the effect of alpelisib in TIE2-mutated VM patients, including drug efficacy, safety data and drug pharmacokinetic (PK).

Methods

Inclusion criteria

Patients with a symptomatic VM harboring *TEK* mutation (obtained with profound biopsy performed in interventional radiology) with resistance, partial response, or contraindication to sirolimus.

Study drug and concomitant treatment

Alpelisib (BYL719; Piqray®) was obtained through Novartis's compassionate drug access program. Initial daily oral doses were 50mg for patients < 50 kg and 100mg for > 50 kg and were titrated in cases with poor response. Sirolimus was discontinued a week prior to alpelisib start, and enoxaparin was started concomitantly to prevent thrombotic complications with sirolimus discontinuation.

Evaluation of drug response and PK

VM extension was documented by MRI and medical photography before and 6 months after alpelisib start. Bloodwork was performed prior and at least monthly (CBC with differential, lipase, glucose and glycosylated hemoglobin, liver profile including GGT, urea, creatinine, coagulation profile). Electrocardiography, cardiac echography, and lung function tests were obtained prior and after 6 months of treatment. Plasma concentrations were measured at 6 months (timing of blood levels: before alpelisib and 0.5, 1, 1.5, 2, 3, 6, 8h after). Alpelisib blood concentrations were determined with High Performance Liquid Chromatography (HPLC) as previously reported (9). 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 non-compartmental analysis (Phoenix version 8.1.0.3530, Certara, USA).

Adverse events

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

Ethics

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

Results

Patient phenotypes

Three patients with TIE2-mutated VM (*TEK* p.L914F) were enrolled(8):

Patient 1: 16-year-old girl (60kg) with an extensive leg VM infiltrating skin, subcutaneous tissues, muscles and joints, and suffering profound LIC (Fig. 1). She suffered profound LIC with platelets < 100* × 10^9 and fibrinogen < 1g/L, that clinically manifested with a tense and painful lower limb with recurrent painful phleboliths and superficial thrombophlebitis. She was wheel-chair dependent due to limited lower limb function and suffered constant pain interfering with sleep and daily activities. She presented a life-threatening bleeding after a minor hymenal septum surgery, with new onset disseminated coagulopathy, was admitted to the PICU and treated with multiple blood products and heparin infusion. The bleeding stopped after 2 weeks. Her disease was resistant to all available treatment options including a six-month course of systemic sirolimus(10) (trough levels: 10-15ng/mL) that induced hypertriglyceridemia (3.5–5.5 mmol/L) but did not lead to any clinical improvement and coagulopathy remained unchanged (Fig. 2). A novel personalized targeted treatment was highly needed for this teenager with life-threatening and treatment-resistant disease.

Patient 2: 12-year-old boy (43kg) displaying an extensive VM of both legs, thorax and right arm associated with profound LIC (platelets < 100* × 10^9; fibrinogen < 1g/L) that led to an extensive left lower leg thrombosis. Systemic sirolimus was initiated as an alternative to long-term anticoagulation (trough levels: 8-12ng/mL) and he remained on this treatment for 3 years. On sirolimus, LIC slowly improved (Fig. 2); nevertheless, there was no observed radiological response and his equinus deformity progressed. Adverse effects from sirolimus were chronic proteinuria and hypercholesterolemia(11).

Patient 3

18-year-old boy (92kg) with an extensive VM of his left leg leading to chronic pain and significant functional impairment disrupting daily activities. He was referred to our multidisciplinary vascular anomalies' team as he remained highly symptomatic despite multiple debulking surgeries and a 6-month-course of subcutaneous enoxaparin. Pain started at the age of 8 and progressively restricted his activity tolerance to 5 minutes due to unbearable pain. He had mild coagulopathy with increased D-dimer (> 2 ug/mL), normal fibrinogen and normal platelets. He had concomitant IgA glomerulonephritis that contraindicated the use of systemic sirolimus.

Treatment response

Pain (concerns patients 1 and 3)

After a month of treatment, patient 1 managed to stop all analgesics and improved mobility. Patient 3's walking capacity increased from 5 minutes to unlimited distance after 3 months, and he recovered normal daily functioning, but pain remained unchanged when standing still.

Coagulopathy (concerns patients 1 and 2)

In patients with severe LIC, coagulation studies showed dramatic improvements (Fig. 1). D-dimer remained increased in all patients (> 2 ug/mL).

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 (Fig. 1). Arm compressive garments for patient 2 were downsized. Joint mobility did not significantly improve in any patient.

MRI imaging

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

Drug exposure

AUC and other PK parameters showed high inter-individual variability (Fig. 2).

Safety and adverse events

Adverse events associated to alpelisib treatment included an episode of self-resolved headache with normal cerebral CT 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 and proteinuria resolved after sirolimus discontinuation (Fig. 2c).

Discussion

We describe the first use of alpelisib in *TIE2*-mutated severe VM. Alpelisib is approved for *PIK3CA*-mutated breast cancer(12). Efficacy in *PIK3CA*-mutated vascular anomalies has previously been shown (PROS(13) and lymphatic malformations(14)). 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. Whether initiating alpelisib prior to joint retraction could prevent this complication remains to be determined.

The clinical VM improvement on alpelisib of sirolimus partial- or non-responders is in line with the *in vitro* data in *TIE2*-mutated VM showing superiority of alpelisib over sirolimus(1). 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.

Some sparse PK data in 2 infants with PROS have previously been reported (trough level and 3 hours after dose)(15). 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)(13, 14). As weight represents the main determinant of drug exposure in children(16), 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) (Fig. 2). 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, sirolimus' adverse effects completely resolved. Exposure to higher doses is unlikely to induce significant toxicity as the AUC on maximal tolerated dose in adults with cancer are significantly higher than in our patients (39500 ng*h/ml (range: 5210–81700 ng*h/ml); 350–400 mg daily)(17–19).

The main limitation of the current study is the limited number of treated patients that hinders definitive conclusions on efficacy and safety of alpelisib in VM.

Conclusion

The first data on alpelisib in TIE2-mutated VM are promising. Instead of a fixed dose, dosing needs to be individualized to patient's characteristics and guided by plasma drug exposure.

Abbreviations

HPLC: High Performance Liquid Chromatography

ISSVA: International Society for the Study of Vascular Anomalies

LIC: localized intravascular coagulopathy

PK: pharmacokinetics

VM: venous malformation

Declarations

Ethics approval and consent to participate: The compassionate use was approved by the Institutional Review Board. All patients provided informed consent.

Consent for publication

All patients provided informed consent for the data presented.

Availability of data and materials

All data generated or analysed during this study are included in this published article. The data analysed during the current study are not publicly available in order to protect personal data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Funding was received by Mitacs Globalink, Unité de recherche en pharmacologie, Research Center CHU Sainte-Justine (start-up funds)

Alpelisib was offered on a compassionate basis by Novartis, Basel

Authors' contributions:

Amandine Remy adapted alpelisib dosing technique from available literature, determined alpelisib blood level, analyzed the PK data, designed the figures and revised the manuscript. Thai Hoa Tran provided counselling on compassionate drug management and interpretation of the data and revised the manuscript. Josée Dubois reviewed the follow-up protocol, interpretated the radiological response and revised the manuscript. Paul Gavra supervised PK data analysis and revised the manuscript. Chantal Lapointe followed the patients, interpreted mobility improvement, and revised the manuscript. Rochelle Winikoff managed follow-up of coagulopathy and interpretation of the data and revised the manuscript. Facundo Garcia-Bournissen participated to the creation of the follow-up protocol, interpretation of PK data and revised the manuscript. Yves Théorêt participated to the follow-up protocol, supervised the adaptation of alpelisib dosing from available literature and alpelisib blood level determination and revised the manuscript. Niina Kleiber followed the patients which motivated alpelisib demand via the compassionate use program based on the exposed rational, designed the follow-up protocol, interpretated the data and wrote the manuscript.

Acknowledgements

Not applicable

References

1. Limaye N, Kangas J, Mendola A, Godfraind C, Schlögel MJ, Helaers R, et al. Somatic Activating PIK3CA Mutations Cause Venous Malformation. American journal of human genetics. 2015;97(6):914-21.
2. Uebelhoer M, Nätynki M, Kangas J, Mendola A, Nguyen HL, Soblet J, et al. Venous malformation-causative TIE2 mutations mediate an AKT-dependent decrease in PDGFB. Human molecular genetics. 2013;22(17):3438-48.
3. Cai Y, Schrenk S, Goines J, Davis GE, Boscolo E. Constitutive Active Mutant TIE2 Induces Enlarged Vascular Lumen Formation with Loss of Apico-basal Polarity and Pericyte Recruitment. Scientific reports. 2019;9(1):12352.
4. Dompmartin A, Acher A, Thibon P, Tourbach S, Hermans C, Deneys V, et al. Association of localized intravascular coagulopathy with venous malformations. Archives of dermatology. 2008;144(7):873-7.
5. Kleiber N, Gariépy-Assal L, Coulombe J, Marcoux S, Essouri S, McCuaig C, et al. Off-Label Use and Safety of Drug Use in Vascular Anomalies. Dermatology. 2021;237(4):649-57.
6. Marcoux S, Théorêt Y, Dubois J, Essouri S, Pincivy A, Coulombe J, et al. Systemic, local, and sclerotherapy drugs: What do we know about drug prescribing in vascular anomalies? Pediatric blood & cancer. 2021:e29364.
7. Seront E, Van Damme A, Boon LM, Vikkula M. Rapamycin and treatment of venous malformations. Curr Opin Hematol. 2019;26(3):185-92.
8. Limaye N, Wouters V, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, et al. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. Nature genetics. 2009;41(1):118-24.
9. Seo SW, Kim JM, Han DG, Geum D, Yun H, Yoon IS. A sensitive HPLC-FLD method for the quantification of alpelisib, a novel phosphatidylinositol 3-kinase inhibitor, in rat plasma: Drug metabolism and pharmacokinetic evaluation in vitro and in vivo. Journal of chromatography B, Analytical technologies in the biomedical and life sciences.2021;1163:122508.
10. Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, et al.Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. The Journal of clinical investigation. 2015;125(9):3491-504.
11. Canaud G, Bienaimé F, Viau A, Treins C, Baron W, Nguyen C, et al. AKT2 is essential to maintain podocyte viability and function during chronic kidney disease. Nature medicine. 2013;19(10):1288-96.
12. Markham A. Alpelisib: First Global Approval. Drugs. 2019;79(11):1249-53.
13. Venot Q, Blanc T, Rabia SH, Berteloot L, Ladraa S, Duong JP, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Nature. 2018;558(7711):540-6.

14. Delestre F, Venot Q, Bayard C, Fraissenon A, Ladraa S, Hoguin C, et al. Alpelisib administration reduced lymphatic malformations in a mouse model and in patients. Sci Transl Med. 2021;13(614):eabg0809.
15. Morin G, Degrugillier-Chopinet C, Vincent M, Fraissenon A, Aubert H, Chapelle C, et al. Treatment of two infants with PIK3CA-related overgrowth spectrum by alpelisib. J Exp Med. 2022;219(3).
16. Admiraal R, van Kesteren C, Boelens JJ, Bredius RG, Tibboel D, Knibbe CA. Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. Archives of disease in childhood. 2014;99(3):267-72.
17. Juric D, Rodon J, Tabernero J, Janku F, Burris HA, Schellens JHM, et al. Phosphatidylinositol 3-Kinaseα-Selective Inhibition With Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study.J Clin Oncol. 2018;36(13):1291-9.
18. Juric D, Janku F, Rodón J, Burris HA, Mayer IA, Schuler M, et al.Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol. 2019;5(2):e184475.
19. James A, Blumenstein L, Glaenzel U, Jin Y, Demailly A, Jakab A, et al. Absorption, distribution, metabolism, and excretion of [(14)C]BYL719 (alpelisib) in healthy male volunteers. Cancer chemotherapy and pharmacology. 2015;76(4):751-60.

Figures

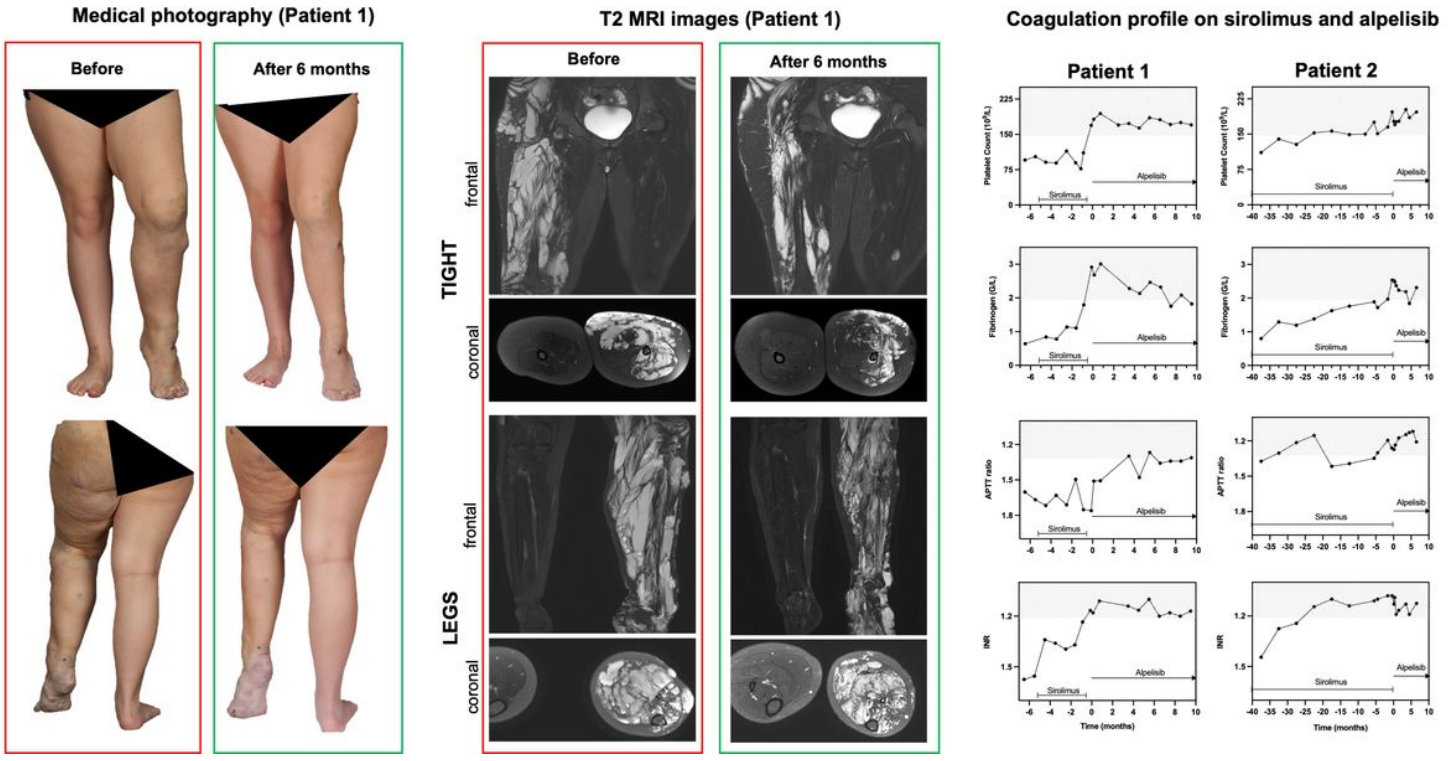


Figure 1

Pharmacodynamics of alpelisib: evolution of clinical, radiological and coagulopathy

(a) Photographs of lower limbs before and after 6 months of treatment (Patient 1)

(b) T2 MRI imaging of lower limbs before and after 6 months of treatment (Patient 1)

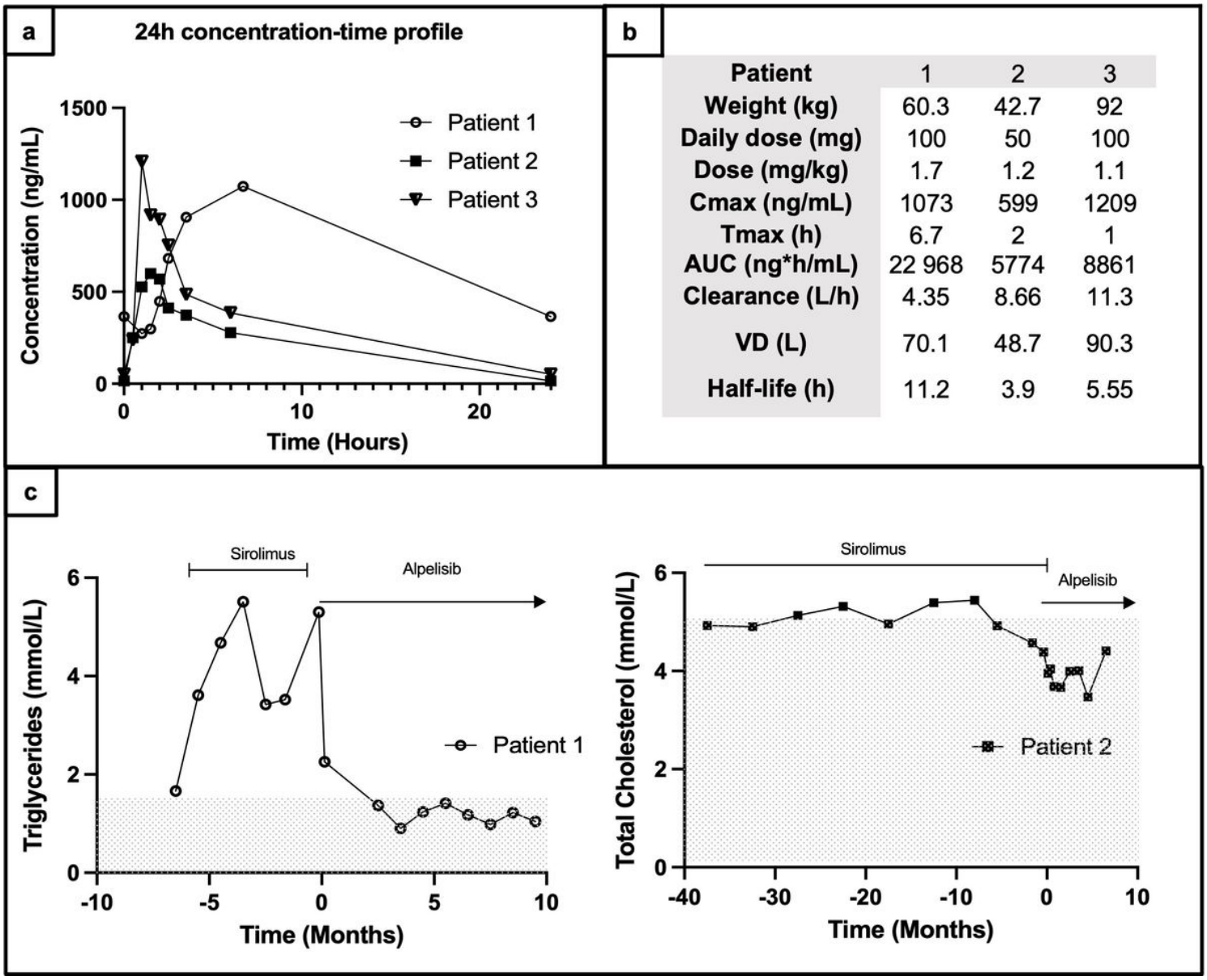
(c) Coagulation profile on sirolimus and alpelisib (Patient 1 and 2)

Legends:

APTT: Activated Partial Thromboplastin Time

INR: International Normalized Ratio

Shaded area corresponds to normal range.



Patient	1	2	3
Weight (kg)	60.3	42.7	92
Daily dose (mg)	100	50	100
Dose (mg/kg)	1.7	1.2	1.1
Cmax (ng/mL)	1073	599	1209
Tmax (h)	6.7	2	1
AUC (ng*h/mL)	22 968	5774	8861
Clearance (L/h)	4.35	8.66	11.3
VD (L)	70.1	48.7	90.3
Half-life (h)	11.2	3.9	5.55

Figure 2

Pharmacokinetics of alpelisib in the study population and lipid profile

(a) 24h concentration-time profile

(b) PK parameters of alpelisib

(c) Lipid profile on sirolimus and later alpelisib

Legends:

AUC: Area Under the Curve

VD: Volume of Distribution