

Medical Management of Vascular Anomalies



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KEYWORDS

• Medical management • Targeted therapies • Coagulopathy

KEY POINTS

- Mutations in PI3K-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) and RAS-RAF-MEK-ERK signaling pathways have now been identified as the cause of many vascular anomalies.
- Sirolimus, an mTOR inhibitor, is the most commonly used agent for medical management of vascular anomalies.
- Alpelisib, a PI3K inhibitor, and trametinib, a MEK inhibitor, are being increasingly used for management of vascular anomalies.
- Identifying and treating coagulation abnormalities, especially perii-periprocedurally, is key to preventing hemorrhagic and thromboembolic complications.
- Future directions include development of more specific inhibitors and combination therapies supported by expanding genetic testing.

INTRODUCTION

Vascular anomalies are broadly classified into vascular tumors and vascular malformations.¹ Molecular diagnosis, in addition to clinical and radiologic features, is now a major component of diagnosis and management of vascular anomalies.² This has led to use of targeted therapies by hematologists/oncologists and other vascular anomalists for medical management of complex, life-threatening and deforming vascular anomalies.^{3,4}

The 2 major signaling pathways responsible for causing vascular anomalies include the following:

1. Phosphoinositide 3-kinase (PI3K)-AKT-mTOR signaling pathway, which is associated with various venous and lymphatic malformations as well as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-related overgrowth syndrome (PROS).
2. Rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase

(MEK)-extracellular signal-regulated kinase (ERK) signaling pathway, which is associated with fast-flow lesions like arteriovenous malformation (AVM) and capillary malformation-arteriovenous malformation (CM-AVM), as well as complex lymphatic malformations like kaposiform lymphangiomatosis (KLA) and Gorham Stout disease (GSD).

With identification of these pathways and associated genetic mutations, we are now able to use agents like mTOR inhibitors—sirolimus and everolimus, MEK inhibitor—trametinib, and PI3K inhibitor—alpelisib as first-line therapies for the management of vascular anomalies (**Fig. 1**).

mTOR Inhibitor: Sirolimus

Mechanism of action

Use of sirolimus in patients with tuberous sclerosis, with mutations identified in the PI3K-AKT-mTOR pathway, prompted its use in the management

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Abbreviations	
AKT	protein kinase B
aPTT	activated partial thromboplastin time
AVM	arteriovenous malformation
BRBNS	blue rubber bleb nevus syndrome
CBC	complete blood count
CCLA	central conducting lymphatic anomaly
CK	creatinine kinase
CLAPO	capillary malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial/generalized overgrowth
CLOVES	congenital lipomatous overgrowth, vascular malformations, epidermal nevi, >scoliosis/skeletal and spinal syndrome
CM-AVM	capillary malformation - arteriovenous malformation
DCMO	diffuse capillary malformation with overgrowth
DIC	disseminated intravascular coagulopathy
DOACs	direct oral anticoagulants
DVT	deep vein thrombosis
ERK	extracellular signal-regulated kinase
FAVA	fibroadipose vascular anomaly
FIL	facial infiltrating lipomatosis
GSD	Gorham Stout disease
KHE	kaposiform hemangioendothelioma
KLA	kaposiform lymphangiomatosis
KMP	Kasabach-Merritt phenomenon
KRAS	Kirsten rat sarcoma
KTS	Klippel-Trenaunay syndrome
LFTs	liver function tests
LIC	localized intravascular coagulopathy
MAP2K	mitogen activated protein kinase MEK1
MAPK	mitogen activated protein kinase
MCM	macrocephaly- capillary malformation syndrome
MEK	mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
NRAS	neuroblastoma rat sarcoma
PE	pulmonary embolism
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PJP	pneumocystis jirovecii pneumonia
PROS	PIK3CA related overgrowth syndromes
PT	prothrombin time
PTEN	Phosphate and Tensin homolog
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma
TIE2	angiopoietin-1 receptor
VTE	Venous thromboembolism

of a child with refractory kaposiform hemangioendothelioma (KHE) with Kasabach-Merritt phenomenon (KMP).^{5,6} The improvement in coagulopathy, the tumor size, pain and functionality with sirolimus led to a phase 2 trial assessing the efficacy and safety of sirolimus in complex vascular anomalies.⁷ Inhibition of downstream signaling in endothelial cells in the PI3K-AKT-mTOR pathway leads to stabilization and/or reduction in the vascular anomalies. This has made mTOR inhibition fundamental in the management of vascular tumors like KHE, angiopoietin-1 receptor (TIE2)-associated complex venous malformations and blue rubber bleb nevus syndrome (BRBNS), phosphate and tensin homolog (PTEN) Hamartoma syndrome, and PIK3CA-associated isolated lymphatic malformations, some complex lymphatic malformations and syndromes including congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), Klippel-Trenaunay syndrome (KTS), and fibroadipose vascular anomaly (FAVA).³

Sirolimus is the most commonly used mTOR inhibitor for the management of vascular anomalies. It is administered orally, with hepatic and intestinal metabolism and biliary/fecal elimination.⁸ Monitoring is through measurement of serum trough levels. However, in infants and children, there can be a wide variation in the metabolism and elimination of sirolimus.⁹ This, along with the vast array of vascular anomalies for which sirolimus is used, make it essential to monitor trough levels.

Goals of treatment

These are varied, given the heterogeneity of the vascular anomalies for which sirolimus is used, ranging from symptom management for pain, swelling, leaking, bleeding, to prevention of complications like cellulitis and sepsis secondary to infections, to organ dysfunction from compression/obstruction of involved and surrounding areas, particularly with large cervicofacial and abdominal malformations.

Dosing

Sirolimus dosing is dependent on the age of the patient and the goal trough level. Generally, starting dose for infants and children is twice a day, and it is once a day for adults. There are excellent guidelines available for dosing. This starting dose is 0.4 mg/m²/dose for infants and 0.8 mg/m²/dose for children and adults.^{7,10} Monitoring of serum trough levels is recommended every 1 to 3 months, with dosing adjusted based on symptoms, side effects and goal trough levels. Of note, infants need serum trough monitoring every

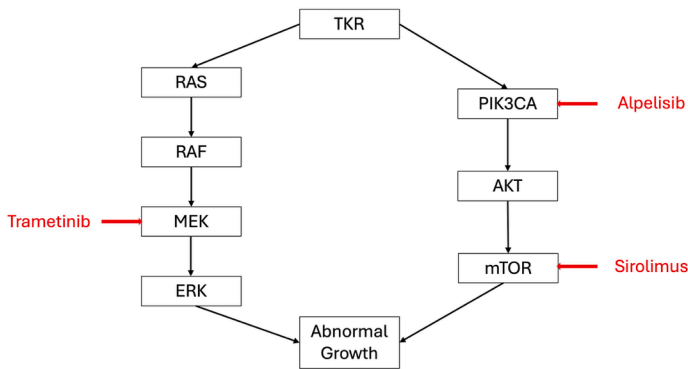


Fig. 1. Commonly described genetic mutations and targeted medications for management of vascular anomalies. (Modified from Greene, Goss-Plast Reconstr Surg. 2018 May.)

3 to 7 days till a stable level is achieved, to ensure that the sirolimus level is not supratherapeutic, due to the variation in their metabolism. Low-risk vascular malformations like isolated lymphatic malformations frequently respond to lower trough levels of less than 6 ng/mL. Malformations with moderate severity can be managed with trough levels 6 to 10 ng/mL, and complex, severe malformations like KHE with KMP and KLA are managed with goal troughs 10 to 13 ng/mL.³

Adverse effects

Common short-term, dose-dependent side effects include mucositis, headaches, rashes, cytopenias, gastrointestinal disturbances, hyperlipidemia, menstrual irregularity, immunosuppression, and impaired wound healing. Rare but serious side effects include peripheral edema, pneumonitis, azoospermia, increased incidence of lymphoma and skin cancers.¹¹ Long-term use has not been associated with major hematologic, renal, or hepatic issues.¹²

Special considerations

Most institutional guidelines for sirolimus-related immunosuppression are based on its use in solid organ transplant. mTOR inhibition is associated with inhibition of CD4⁺ T-cell differentiation,¹³ making opportunistic infection like *Pneumocystis jirovecii* pneumonia (PJP) a potential complication of long-term sirolimus management, especially with trough levels greater than 10 ng/mL, in infants with immature immune systems, malformations causing protein loss leading to hypogammaglobulinemia and when combined with other immunosuppressive agents like long-term steroids. As a result, prophylaxis against PJP should be reviewed with these high-risk patients based on institutional guidelines (DIC).¹⁴

Additionally, there remains a paucity of evidence regarding administration of live vaccines while on long-term sirolimus therapy. If possible, live

vaccines should be administered prior to initiation of sirolimus therapy. If delaying the administration of live vaccines is considered, this should be reviewed with family based on institutional guidelines, underlying vascular anomaly as well as anticipated duration of sirolimus treatment.¹⁴

Monitoring while on sirolimus

This is based on severity of disease and trough goals: baseline and on-therapy monitoring every 1 to 3 months includes—vital signs including height, weight, and blood pressure; laboratory monitoring including complete blood count (CBC) with differential, chemistries including liver function tests (LFTs) and creatinine, lipid profile, and sirolimus trough (after initiating treatment).

PI3K Inhibitor: Alpelisib

Mechanism of action

Activation of PI3K signaling pathway and downstream activation of effectors has been identified in various conditions, giving rise to these disorders now being pooled under the term PROS. However, not all conditions associated with mutations in PI3K are associated with overgrowth. PIK3CA-related vascular anomalies include isolated lymphatic and venous malformations, as well as overgrowth syndromes like CLOVES, KTS, diffuse capillary malformation with overgrowth (DCMO), macrocephaly-capillary malformation syndrome (MCM), capillary malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial/generalized overgrowth (CLAPO), and facial infiltrating lipomatosis (FIL).¹⁵ Mutation in PIK3CA has also been seen in complex lymphatic anomalies like generalized lymphatic anomaly.¹⁶ Identification of somatic mutations in the PI3K signaling pathway has led to increasing use of alpelisib in various vascular anomalies. Improvement in symptoms with PI3K inhibition was first demonstrated by Venot and colleagues¹⁷ in 2018. Since then, PI3K

inhibitor alpelisib has been Food and Drug Administration-approved for the management of patients with PROS in children aged greater than 2 years.¹⁸

Goals of treatment

Management of pain, swelling, and prevention of complications, with increasing use not only in malformations with lipomatous overgrowth but also in isolated venous and lymphatic malformations. In patients with poor response to sirolimus therapy, alpelisib offers an alternative therapeutic option. Of note, the immunosuppression seen with sirolimus is not seen with alpelisib.

Dosing

Alpelisib is usually started orally at a daily dose of 50 mg for those aged 2 years to less than 6 years, 125 mg for those aged 6 to less than 18 years, and 250 mg for adults (Novartis NCT06997588), with a maximum dose of 250 mg daily in adults.¹¹ Unlike sirolimus, there are no trough levels for alpelisib. Dosing is adjusted based on response and side effects.

Adverse effects

Common short-term side effects include rash, hair thinning, gastrointestinal disturbance like diarrhea, hyperglycemia, transaminitis, headache, fatigue, and cytopenia.¹¹ Long-term effect on growth and hyperglycemia needs further evaluation.

Special considerations

Alpelisib does not cause immunosuppression, hence PJP prophylaxis is not required. Alpelisib is contraindicated during pregnancy and breast-feeding.

Monitoring while on alpelisib

Baseline investigations include electrocardiogram, echocardiogram; vital signs including height, weight, and blood pressure; laboratory monitoring including CBC with differential, chemistries including LFTs and creatinine, lipid profile, pancreatic enzymes amylase and lipase, serum glucose, and hemoglobin A1C. Clinical evaluation, vital sign and growth monitoring, laboratory evaluations and electrocardiogram are recommended every 3 months initially, followed by every 3 to 6 months while on therapy.

MEK Inhibitor: Trametinib

Mechanism of action

Somatic mutations in mitogen activated protein kinase MEK1 (MAP2K1),¹⁹ with the activation of the RAS/mitogen activated protein kinase (MAPK)²⁰ is responsible for various malformations, including fast-flow lesions like AVM and CM-AVM, complex

lymphatic anomalies like KLA associated with neuroblastoma rat sarcoma (NRAS), GSD, and central conducting lymphatic anomaly (CCLA) associated with kirsten rat sarcoma (KRAS).²¹ Identification of these somatic mutations has led to increasing use of MEK inhibitor trametinib for vascular malformations associated with the RAS-RAF-MEK-ERK signaling pathway.

Goals of treatment

Treatment is aimed at stabilization/prevention of disease progression, as well as control of complications like pain, bleeding (often with no or minor trauma) seen with fast-flow lesions.

Dosing

Trametinib is administered orally at a daily dose of 0.0125 to 0.025 mg/kg/dose in children, and 0.5 to 2 mg in adults.

Adverse effects

Common short-term side effects include rash, paronychia, gastrointestinal disturbance, hypertension, and edema. Rare but serious side effects include bleeding, rhabdomyolysis, retinal detachment, and retinal vein occlusion and cardiac toxicity including cardiomyopathy and bradycardia.¹¹

Special considerations

Trametinib is contraindicated during pregnancy and breast-feeding.

Monitoring while on trametinib

Investigations at baseline and every 3 to 4 months while on therapy include vital signs including height, weight, and blood pressure; laboratory monitoring including CBC with differential, chemistries including LFTs and creatinine, creatinine kinase level, echocardiogram, ophthalmologic evaluation including retinal examination. Once on a stable dose, cardiac and ophthalmologic evaluations can be made less frequent, to every 6 months followed by yearly, as long as they are within normal range.

COAGULOPATHY IN VASCULAR ANOMALIES

Coagulation abnormalities in vascular anomalies can range from isolated thrombocytopenia to extensive thromboembolism causing deep vein thrombosis and pulmonary embolism. An understanding of these abnormalities and associated complications along with timely evaluation by a hematologist is essential not only for symptom management but also for the prevention of life-threatening bleeding or thrombosis, especially in the periprocedural setting.

Consumptive Coagulopathy

This can be seen with fast-flow lesions and can vary in severity based on underlying vascular anomaly and mechanism of consumption of coagulation factors. In congenital hemangioma, the coagulopathy is usually transient, and is secondary to thrombus formation within the lesion. In contrast, the coagulopathy is KHE with KMP is profound, with trapping of platelets and fibrinogen within the lymphatics. Although not a fast-flow lesion, KLA can also be associated with prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), profound thrombocytopenia and hypofibrinogenemia.^{14,22}

Localized Intravascular Coagulopathy and Venous Thromboembolism

Venous ectasia, chronic venous stasis as well as activation of fibrinolysis secondary to vascular abnormalities in slow-flow malformations and malformations with a large venous component may be associated with localized intravascular coagulopathy (LIC). This, in turn, can be associated with the formation of phleboliths, which may be painful, as well as bleeding from unaffected areas. Endothelial injury from endovascular procedures, and immobility secondary to these procedures can further compound the risk of venous thromboembolism (VTE). Rarely, LIC can progress to disseminated intravascular coagulopathy (DIC).¹⁴

Anticoagulation in Vascular Anomalies

Goals of treatment

One goal includes symptom management like control of pain, swelling, and bleeding. Mack and colleagues²³ demonstrated the improvement in quality of life with anticoagulation in patients with slow-flow vascular malformations.

Another role on anticoagulation is prevention of VTE in malformations with large ectatic veins and optimization of periprocedural management to prevent hemorrhage and/or thromboembolism. Although no guidelines exist for anticoagulation around procedures, it is generally recommended to assess for risk factors like personal and family history of thrombosis, fibrinogen level less than 100 mg/dL, platelet count less than 150,000 mm³ and presence of large, ectatic veins. Because d-dimer can be chronically elevated in various vascular anomalies, it is not a reliable marker when used in isolation for the evaluation of thrombotic risk.^{24,25}

Commonly used agents

Low molecular weight heparin, aspirin, and more recently direct oral anticoagulants (DOACs) are

used in an outpatient setting.²⁶ Unfractionated heparin can be used periprocedurally while inpatient. It is recommended that anticoagulation be initiated 1 to 2 weeks prior to procedure based on laboratory evaluation and presence of risk factors. Anticoagulation may be continued without any doses held for minor procedures. For procedures that carry a higher risk, anticoagulation may need to be discontinued 24 hours prior to procedure. Postprocedure anticoagulation may be needed especially in patients with LIC secondary to extensive slow-flow malformations. Supportive agents like cryoprecipitate may be needed perioperatively.²⁴ Multidisciplinary approach is needed to optimize periprocedural management of complex vascular anomalies.

Monitoring while on chronic anticoagulation

Investigations at baseline and every 3 to 4 months while on therapy include monitoring of vital signs including height, weight, and blood pressure; laboratory monitoring including CBC with differential, chemistries including LFTs and creatinine, coagulation profile including PT, aPTT, fibrinogen, and d-dimer. Although there is limited data on the effect of long-term anticoagulation on bone density in children, monitoring is recommended especially in children with low body mass index.^{27,28}

OTHER THERAPIES

Besides targeted therapies, various other medications play an important role in management of vascular anomalies. Beta-blockers like systemic propranolol and topical timolol are used for the treatment of infantile hemangiomas.²⁹ Steroids, usually in combination with agents like sirolimus or vincristine, play a critical role in the management of KHE with KMP.³⁰ Nonsteroidal anti-inflammatory agents like ibuprofen, and analgesics like acetaminophen are important for symptom control for pain related to vascular anomalies. It is essential to review the safe use of agents like aspirin and ibuprofen, especially in the setting of coagulopathy. Broad-spectrum antibiotics are essential for the management of cellulitis and sepsis. Trimethoprim-sulfamethoxazole is the most commonly used antibiotic for PJP prophylaxis. Gastrointestinal bleeding, the most common complication of BRBNS,³¹ can be associated with chronic iron deficiency anemia, necessitating intravenous iron supplementation. Iron supplementation, either oral or intravenous, may also be needed in AVM associated with frequent bleeding. Bisphosphonates are often used in combination with sirolimus in complex lymphatic anomalies.³²

FUTURE DEVELOPMENTS

With easier accessibility of somatic and germline genetic testing options, medical management of vascular anomalies continues to advance. In addition to commonly used agents discussed earlier, we now have more specific PI3K inhibitors, other MEK inhibitors, AKT inhibitors, and antiangiogenic agents like bevacizumab, thalidomide, and pazopanib being studied, while we continue to develop more specific inhibitors of PIK3CA and TIE2. Combination therapies to maximize benefit while limiting adverse effects are also being evaluated.

SUMMARY

Molecular diagnosis has now made targeted therapy an important management option for vascular anomalies, often first-line, and frequently in combination with surgical and interventional treatments. However, there remains a need for the development of more specific agents, as we continue to study long-term effects of these therapies.

CLINICS CARE POINTS

- PI3K-AKT-mTOR and RAS-RAF-MEK-ERK signaling pathways are commonly associated with the development of vascular anomalies.
- Referral to hematology-oncology for evaluation of targeted therapeutic options should be considered early in management.
- Close clinical and laboratory monitoring is essential for patients on medical therapies.
- Evaluation and management of coagulopathy, especially periprocedurally, is critical for complex vascular anomalies to avoid bleeding and thromboembolic complications.

DISCLOSURE

T. Shah is an investigator for Merck, Novartis and Relay Therapeutics, and has consulted for Novartis. D.M. Adams is a consultant and investigator for Novartis, Relay, Kaken pharmaceuticals.

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