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The Role of Medical Management in Vascular Anomalies

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Abstract

Historically, the care for patients with vascular anomalies has been challenging due to the complex nature and diversity of these anomalies with a wide array of symptomatology. In the recent past, most therapies for vascular anomalies focused on surgical, procedural, and supportive care measures to treat local symptoms, but many patients still experienced significant disease with excess morbidity and mortality. Today, the pharmacotherapeutic options available for treating vascular anomalies have greatly expanded due to the increased understanding of the genetic and molecular pathways causing these anomalies, with the subsequent development of more targeted pharmacotherapies. In addition to the growth in targeted medications available to treat patients with vascular anomalies, there has been an improved understanding of the hematologic abnormalities related to these diseases and how to manage them. While interventional radiologists do not typically primarily manage systemic medications to treat vascular anomalies, a baseline understanding of the medical management of these diseases is essential to ensuring that a contemporary, multidisciplinary, multimodal approach to treatment is pursued when appropriate. Ultimately, patients are now benefitting from having multiple modalities of treatments available to them and are experiencing improved quality of life and less morbidity.

Keywords
- alpelisib
- sirolimus
- vascular anomalies
- hematology
- interventional radiology

The care of patients with vascular anomalies has historically been challenging for many reasons, beginning with the complex and diverse nature of these anomalies. A limited knowledge of the underlying mechanism of disease has made it difficult to ultimately guide the specific care of these anomalies, resulting in a lack of a unified approach to managing patients with both simple and complex vascular anomalies. Additionally, the wide-ranging clinical and symptomatic diversity of vascular anomalies that affect all systems of the body require individualized care with careful consideration of the many modalities of therapy.[1] More so, an incomplete understanding of the underlying genetic and molecular mechanisms of disease has resulted in a predominance of surgical, procedural, and supportive care for local symptoms with a deficiency of specific, systemic pharmacotherapies available to target the disease process. The current treatment options for vascular anomalies have vastly expanded in the past decade due to the increased understanding of the genetic and molecular pathways causing these anomalies, leading to the development and use of targeted pharmacotherapies. These targeted pharmacotherapies provide patients with effective therapies that may be used alone or in combination with other interventions like surgery or sclerotherapy. Today, the multidisciplinary care model allows healthcare providers to utilize dynamic combinations of these therapies, such as sclerotherapy with concomitant medical management, which is now the standard approach in providing comprehensive and up-to-date care for these patients.[2] The purpose of this article is to

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provide interventional radiologists with an updated overview of the expanding role of the medical management of vascular anomalies, with a specific focus on both targeted pharmacotherapies and the medical management of associated hematologic abnormalities.

Targeted Pharmacotherapies in Vascular Anomalies

In the past, the rationale for the use of pharmacotherapeutic agents to treat vascular anomalies and their hematologic manifestations was based on trial-and-error, experimental use, or theoretical benefit. More specific targeted pharmacotherapies are now being thoroughly studied for use in vascular anomalies and have become, or are becoming, first-line treatments for many patients. Driving this change is a deeper understanding of the genetic and molecular pathways involved in the growth and proliferation of vascular anomalies, thus opening the door for the development of targeted pharmacotherapies. Understanding these pathways has also allowed for the repurposing of existing medicines with antiangiogenetic or antineoplastic effects for vascular anomalies.

Review of the TEK/PI3K/AKT/mTOR and RAS/MAPK/MEK Pathways

Vascular anomalies form when there are aberrations in vascular tissue development, leading to the broad phenotypic abnormalities seen in arteries, veins, capillaries, lymphatics, mixed vessels, and soft tissues. The genetic mutations leading to these anomalies exhibit themselves with great phenotypic variance, yet most mutations occur in one of these two cellular pathways: the TEK/PI3K/AKT/mTOR and RAS/MAPK/MEK pathways.[3] There are many artistic renderings of these complicated pathways, but it is important to consider the two pathways themselves and that elements of the two pathways also interact with one another via cross-inhibition and cross-activation.[4] Mutations causing overactivation of either pathway result in cellular dysregulation and cell proliferation in the form of a clinically relevant vascular anomaly or overgrowth syndrome (►**Fig. 1**).[4]

The Implication of Vascular Anomalies and Genotype Testing

There are many clear genotype–phenotype correlations, such as those with Klippel–Trenaunay syndrome (capillary malformation, low-flow malformation, overgrowth) caused

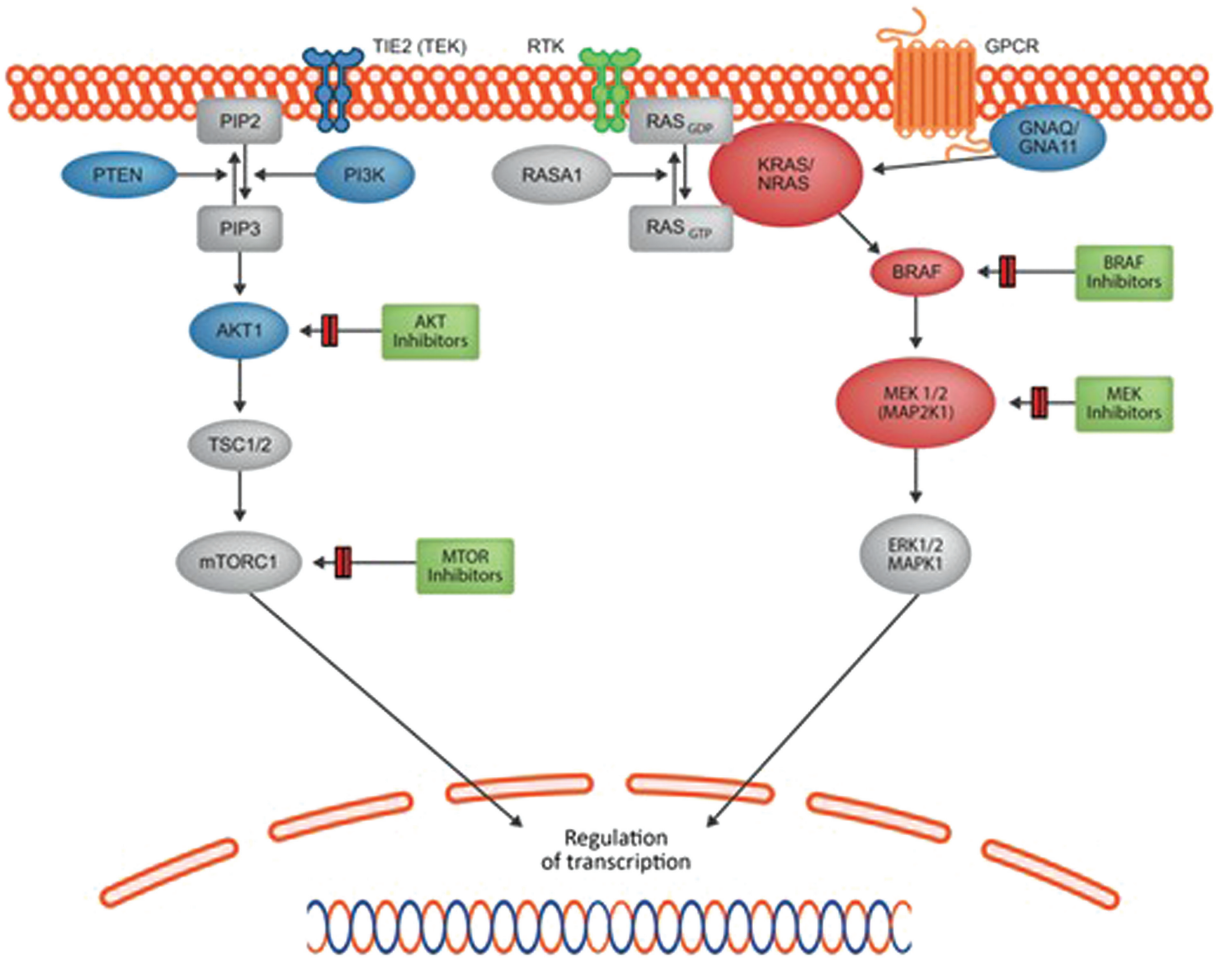

Fig. 1 Schematic overview of commonly affected pathways in vascular anomalies (used with permission from Copyright Clearance Center, Inc.).

by a PIK3CA mutation. In these situations, genetic testing is not always required to initiate targeted pharmacotherapy. Conversely, genetic testing can be of immense importance in confirming the suspected gene mutation, helping to determine the best pharmacotherapy for a patient, and establishing more nuanced genotype–phenotype associations and responses to therapy. More so, further genetic characterization of vascular anomalies will continue to pave the way for ongoing research.

Most vascular anomalies are caused by somatic mutations, and in these cases biopsy of the affected tissue is required for diagnostic yield. The yield of somatic testing in vascular anomalies is limited by many obstacles such as the need for sedation to obtain a biopsy in young children, specimen-type differences, technical limitations, lack of insurance coverage, and the accuracy of conventional genetic testing.[5] Reports show that diagnostic yield is significantly higher with deep depth of coverage compared with low depth of coverage. Additionally, a core biopsy of subcutaneous, lesional tissue tends to produce a higher diagnostic yield compared with skin punch samples.[6] These intricacies highlight the collaborative importance among diagnostic providers, proceduralists, and geneticists.

Sirolimus

Sirolimus (also called rapamycin) is a specific inhibitor of the mammalian target of rapamycin (mTOR) and blocks the activation of downstream kinases in the phosphatidylinositol 3-kinase (PI3K) pathway, which is known to regulate angiogenesis, cell growth, and other cellular processes.[7]

Sirolimus is an oral medication typically dosed at 0.8 mg/m^2 twice daily with goal serum trough levels of around 5 to 15 ng/mL depending on the severity of the clinical symptoms. Oral sirolimus is not approved by the United States Food and Drug Administration (FDA) for vascular anomalies but is used off-label as a first-line therapy for microcystic and complex lymphatic malformations (LMs), Kaposiform hemangioendothelioma (KHE), PTEN-associated vascular anomalies, and many venous malformations (VMs). Sirolimus is well tolerated with no side effects in the majority of infants, children, and adults. Common side effects include mouth sores, nausea or vomiting, headaches, hypertriglyceridemia, liver and kidney injury, and mild T cell immune suppression with the risk for *Pneumocystis jirovecii* pneumonia. Monitoring includes frequent laboratory monitoring of complete blood count (CBC), comprehensive metabolic panel, and lipid profile.

Sirolimus is a good example of how an extrapolated understanding of the mTOR pathway led to its successful use in patients. As the role of angiogenesis by activation of the PI3K/AKT/mTOR pathway was becoming better understood in tumors and vascular anomalies, sirolimus was trialed with clinical success in a patient with refractory KHE and Kasabach–Merritt phenomenon (KMP), as well as in patients with other complicated vascular anomalies.[8] A phase II clinical trial then confirmed the general safety and overall efficacy of sirolimus in patients with various vascular anomalies with lymphatic components, KHE, and PTEN-associated vascular anomalies.[8,9] Other studies in both adults and children also support these early findings and bolstered the use of sirolimus in other types of vascular anomalies.[10]

In addition to the clinical evidence that supports the expanded use of sirolimus in many different types of vascular anomalies, the identification of vascular anomalies with alterations in the TEK/PI3K/AKT/mTOR pathway also provides compelling evidence for its potential use in these anomalies.

There is a growing body of evidence for the expanded use of sirolimus in vascular anomalies that encompass macrocystic and microcystic lymphatic anomalies; combined vascular anomalies with lymphatic components; and complex lymphatic anomalies such as central conducting lymphatic anomaly (CCLA), Gorham–Stout disease (GSD), generalized lymphatic anomaly (GLA), KHE, and PIK3CA-related overgrowth spectrum (PROS) with vascular anomalies.[9]

There is also growing evidence to support the use of sirolimus in congenital VMs. Many VMs are caused by mutations in TEK which encode TIE2 and functions in the TEK/PI3K/AKT/mTOR pathway,[11,12] but there is currently no TIE2 inhibitor approved for human use. Due to its place in the molecular pathway, though, VMs with TEK mutations are often responsive to sirolimus or PIK3CA inhibition, which will be discussed later. These VMs that include isolated VMs, diffuse VMs, and blue rubber bleb nevus syndrome are known to harbor germline or somatic mutations in the TEK/TIE2 pathway.[13,14] In VMs without TEK mutations, however, over half are still reported to have a somatic PIK3CA mutation.[15]

Importantly, the reported clinical outcomes from systemic sirolimus show efficacy in volume reduction, decreased pain symptoms, and improved quality of life. While sirolimus does not typically lead to a complete disease response, the improvement in clinical symptoms that are observed makes sirolimus an excellent option for many patients. In addition, sirolimus may be able to decrease the number and frequency of concomitant sclerotherapy procedures or other surgeries.

Sirolimus has also been shown to be well-tolerated even in the youngest of patients. Sirolimus has been used in the treatment of neonates and has been shown to be well tolerated.[9] In infants with vascular anomalies or tumors that require urgent therapy, as is the case in KHE and some LMs of the head and neck, sirolimus is started at birth. There are also reports of safe use of late prenatal use of sirolimus in mothers with prenatal diagnoses of fetal rhabdomyomas associated with tuberous sclerosis.[16] Prenatal administration of sirolimus for infants with high-risk LMs of the head and neck has also been reported with a reduction in the size of the LM.[17] While oral sirolimus is considered well-tolerated and efficacious, ongoing studies are required to determine the long-term effects when used in infants and children for extended periods of time.

There is growing evidence that systemic everolimus may be an effective alternative to sirolimus in patients with side effects to sirolimus or without access to it.[18]

In the same way that systemic sirolimus shows benefit in vascular anomalies with lymphatic components, topical

application of sirolimus to superficial cutaneous LMs is also reported to be beneficial.[19,20] Ongoing clinical trials are needed to confirm large-scale efficacy and are in process (NCT06239480). Topical therapy could also show benefit in other vascular anomalies with superficial cutaneous involvement if it also harbors a mutation in the TEK/PI3K/AKT/mTOR pathway.

Alpelisib

Alpelisib is an α-selective phosphatidylinositol 3-kinase (PI3K) inhibitor approved for the treatment of *PIK3CA*-mutated breast cancer[21] and PROS disorders. PI3K is downstream from growth factor receptors and part of a pathway that regulates cell growth, development, proliferation, and insulin signaling. In the case of vascular anomalies, somatic mutations lead to overactivation of growth in affected bone, tissue, or vessels.

Alpelisib (VIJOICE, Novartis, NJ) was approved in 2022 specifically for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PROS who require systemic therapy. This approval was made based on the primary outcome of >20% volume reduction in a target lesion in patients with CLOVES syndrome (**c**ongenital **l**ipomatous **o**vergrowth, **v**ascular malformations, **e**pidermal nevi, **s**coliosis/skeletal/spinal anomalies), megalencephaly–capillary malformation polymicrogyria (MCAP), Klippel–Trenaunay syndrome (KTS), facial-infiltrating lipomatosis (FIL), and several other PROS disorders.[22]

Alpelisib is an oral medication given once daily as a tablet or liquid. Dosing is based on age and can be given for an indefinite amount of time. Long-term effects are not known; however, thus monitoring for late effects is important to consider when following patients receiving alpelisib.

The tolerability of alpelisib has shown to be especially favorable, with the most common side effects occurring in up to 5% of patients in the form of severe hypersensitivity, skin rash, hyperglycemia, acute pneumonitis, and diarrhea. In contradistinction to sirolimus, it is not an immunosuppressant and does not increase the risk of infection. Due to the risk for hyperglycemia and rarely liver and kidney injury, frequent laboratory monitoring of the patient's CBC, comprehensive metabolic panel, hemoglobin A1C, amylase, and lipase are recommended.

Alpelisib is indicated for all PROS disorders, such as fibroadipose hyperplasia or overgrowth without vascular anomaly, hemihyperplasia–multiple lipomatosis, CLOVES, macrodactyly, FIL, MCAP, dysplastic megalencephaly, and KTS.[23]

The majority of LMs are PIK3CA-mutated, implicating the use of alpelisib or sirolimus to block this pathway.[24] There are numerous reports of the successful treatment of LMs with alpelisib, and clinical trials evaluating the efficacy and safety of PIK3CA-mutated LMs in children and adults are ongoing (NCT05948943). Patients with fibroadipose vascular anomalies (FAVAs) that are refractory to cryoablation, sclerotherapy, and/or surgery have also been treated with alpelisib when a PIK3CA mutation is identified.[25]

Alpelisib can also be considered for any vascular anomaly with a non-PIK3CA mutation that is within the TEK/PI3K/AKT/mTOR signaling pathway such as VMs with TEK mutations, and venous and/or LMs in patients with Proteus syndrome caused by AKT mutations.

Interestingly, because PIK3CA mutations dysregulate and overactivate the TEK/PI3K/AKT/mTOR pathway, other medications that downregulate this pathway have conceptual reason to be effective in patients receiving alpelisib but are not able to tolerate the drug or treatment becomes ineffective. This includes AKT inhibition with miransertib and mTOR inhibition with sirolimus.

Alternative PIK3CA inhibitors are in development, including drug delivery by alternative routes of administration.

Trametinib

Trametinib is an oral MEK inhibitor that is FDA-approved for use in metastatic melanoma and other BRAF V600E or V600K mutation-positive solid tumors but is also being used off-label for a wide variety of patients with vascular anomalies and associated mutations in the RAS/MAPK/MEK pathway. Identified gene mutations in this pathway include EPHB4, KRAS, HRAS, NRAS, BRAF, RAF1, PTPN11, and SOS1.[26]

Vascular anomalies with signaling defects in this signaling pathway include Noonan's syndrome (PTPN11); complex lymphatic anomalies such as CCLA caused by EPHB4 mutations; sporadic or syndromic arteriovenous malformations (AVMs) caused by MAP2K1/MEK1, KRAS, or EPHB4 mutations; Parkes–Weber syndrome (capillary malformation, arteriovenous fistula or malformation, overgrowth) caused by RASA1 mutations; and Kaposiform lymphangiomatosis (KLA) with NRAS mutations.[27] This is of particular importance to interventional radiologists, as we now have a medical option that can be used concomitantly with endovascular embolization to manage AVMs with one of these somatic mutations.

Mutations in GNAQ and GNA11 that cause capillary malformations (including Sturge–Weber syndrome) also show evidence of increased RAS/MAPK signaling, but it is not yet clear whether MEK inhibition will lead to clinical improvement in these patients.

Trametinib is taken once daily as a tablet or liquid and is dosed by weight and age. The most common side effects reported are edema; skin rash; gastrointestinal disturbance; and abnormalities in blood counts, liver enzymes, and serum albumin levels. Monitoring includes frequent laboratory monitoring of CBC and comprehensive metabolic panel.

Trametinib can be prescribed for patients with vascular anomalies that harbor mutations in this pathway and may be of benefit in patients with refractory or untreatable anomalies. Trametinib can be used for many years, but long-term effects are not yet known. As expected, alternative MEK inhibitors need to be studied to determine their efficacy.

Bisphosphonates

Bisphosphonates (zoledronic acid, pamidronate) are IV medications that work to slow down bone resorption by reducing osteoclast function and improving bone mineral density. These medicines have become essential in the management of complex vascular anomalies, with their successful use as an adjunct therapy alongside sirolimus reported in patients

with bone destruction as a result of GSD, GLA, and KLA.[28] The rationale for their specific use is through nitrogen-containing bisphosphonate effect on the RAS/MAPK pathway that inhibits osteoclast activity and induces osteoclast apoptosis, leading to decreased bone resorption and improved bone density.

Patients are recommended to take daily vitamin D and calcium carbonate, and then receive IV infusions every 2 to 3 months for up to 5 years at a time. Surveillance bone imaging is performed approximately every 6 months and laboratory monitoring occurs every few months with CBC, CMP, ionized calcium, and vitamin D (25-OH). Side effects include infusion reactions, musculoskeletal pain, skin rash, dry mouth, and gastrointestinal disturbances.

Inhibitors of Angiogenesis for Hereditary Hemorrhagic Telangiectasia

After many years of nonuse due to its teratogenicity, thalidomide was shown to be effective in the treatment of gastrointestinal (GI) bleeding from vascular anomalies based on its antiangiogenic and antitumor properties.[29,30] Since then, further studies aimed at the treatment of telangiectasias and bleeding in hereditary hemorrhagic telangiectasia (HHT) have been ongoing, including phase I and II trials investigating the use of pomalidomide treatment for epistaxis and GI bleeding in patients with HHT (NCT02287558, NCT03910244).

Bevacizumab (Avastin) is a monoclonal antibody that acts as a VEGF receptor antagonist and has been studied in HHT to reduce epistaxis and anemia. Results have varied, though; so, follow-up studies are required to determine its benefit.[1]

Future Targeted Therapies

Despite the improvements in quality of life and decreased morbidity and mortality attributed to these therapies, many patients still do not respond to treatment or are living with chronic disease and many comorbidities from their vascular anomaly. Thankfully, the scientific research of vascular anomalies is rapidly expanding with more promising therapeutic agents and drug-delivery mechanisms being developed.

Hematologic Abnormalities Associated with Vascular Anomalies

Vascular anomalies can be associated with hematologic abnormalities of the coagulation system.[31] This can manifest as thrombosis, localized intravascular coagulation (LIC), KMP, or disseminated intravascular coagulation (DIC). While coagulopathy can be asymptomatic and transient in some patients, it can lead to thrombosis, bleeding, and death. Therefore, it is crucial that hematologic abnormalities be considered and identified immediately.

The 2018 International Society for the Study of Vascular Anomalies classification summarizes the hematologic disorders associated with specific vascular anomalies (►**Table 1**).[23] It is imperative for providers to test for hematologic abnormalities with a CBC, fibrinogen level, prothrombin time (PT), activated partial thromboplastin time (aPTT), and d-dimer when there is suspicion for any of these anomalies.[32]

Activation of Coagulation

Vascular anomalies exhibit abnormal vessel architecture that results in altered blood flow, abnormal endothelial cell function, and, in some cases, activation of the coagulation cascade. For example, venous stasis leads to activation of clotting factors, which result in fibrin formation. This fibrin formation can produce a classic blood clot or create fibrin strands that trap platelets, shear red blood cells, and further activation of coagulation (►**Fig. 2**).[33]

Localized Intravascular Coagulation and Thrombosis

LIC is typically described as mild thrombocytopenia, hypofibrinogenemia, and elevated d-dimer, but without the high

Table 1 Hematologic disorders associated with vascular anomalies

Anomalies	Hematological disorders
Tufted angioma Kaposiform hemangioendothelioma	Profound and sustained thrombocytopenia with profound hypofibrinogenemia, consumptive coagulopathy, and elevated D-dimer (Kasabach–Merritt phenomenon)
Rapidly involuting congenital hemangioma	Transient mild/moderate thrombocytopenia, +/− consumptive coagulopathy and elevated D-dimer
Venous malformations/lymphatic-venous malformations	Chronic localized intravascular coagulopathy with elevated D-dimer, +/− hypofibrinogenemia, and +/− moderate thrombocytopenia (may progress to DIC after trauma or operation)
Lymphatic malformations	Chronic localized intravascular coagulopathy with elevated D-dimer and +/− mild to moderate thrombocytopenia (consider *Kaposiform lymphangiomatosis*) (may progress to DIC after trauma or operation)
Multifocal lymphangioendotheliomatosis with thrombocytopenia/cutaneovisceral angiomatosis with thrombocytopenia	Sustained, fluctuating, moderate to profound thrombocytopenia with gastrointestinal tract bleeding or pulmonary hemorrhage
Kaposiform lymphangiomatosis	Mild/moderate thrombocytopenia, +/− hypofibrinogenemia, and D-dimer elevation

Abbreviation: DIC, diffuse intravascular coagulopathy.

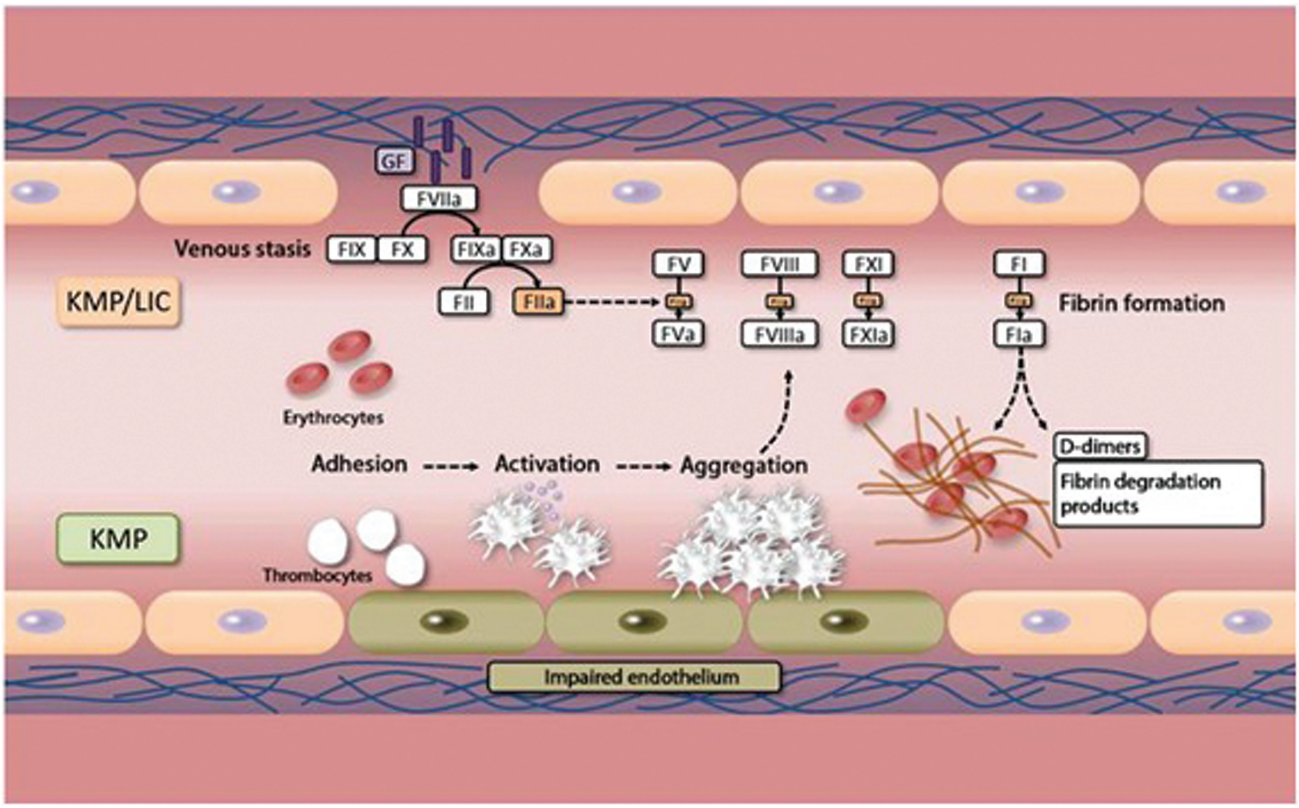

Fig. 2 Activation of coagulation in vascular anomalies.

risk for prolonged PT and PTT and high risk for bleeding. LIC is most likely to be seen in slow-flow vascular malformations such as VMs, LMs, and venous-lymphatic malformations. Venostasis and chronic LIC predispose to deep vein thrombus (DVT) or superficial phlebolith formation, and in turn significant swelling, pain, and morbidity.

Patients who develop DVT are routinely treated with therapeutic anticoagulation. Treatment of chronic LIC with chronic anticoagulation is commonly utilized because it is associated with decreased thrombus formation, improvement in pain caused by phleboliths, and some improvement in laboratory abnormalities. Anticoagulation with low-molecular-weight heparin has been effective in the management of LIC, and is the preferred pharmacotherapy by many.[34] Newer agents such as direct oral anticoagulants (DOACs) are also being used with reported similar efficacy and noninferiority,[35] but further clinical studies are needed to determine which agent, if any, offers more benefit than another. Treatment of LIC with antiplatelet therapies, such as aspirin, may also show benefit. In one study reviewing the patient-perceived benefits of aspirin for LIC in VMs, the majority of patients reported some benefit in their symptoms.[36] Patients with Sturge–Weber syndrome and leptomeningeal angiomatosis do not show laboratory evidence of LIC, but do experience recurrent intracerebral venous thrombosis and venostasis, which then results in neurologic decline. In this setting, aspirin has been shown to stabilize or improve neurologic outcomes[37] and its use is recommended for most patients with confirmed Sturge–Weber syndrome.[38]

In patients with LIC who do not experience the clinical symptoms of pain, swelling, phlebolith formation, or thrombosis, the benefits of using preventative anticoagulation or antiplatelet therapy are not clear. One must carefully weigh the risks of bleeding and other complications when deciding to initiate these therapies.

Indirectly, treatment of the underlying vascular anomaly that leads to its improvement, whether mechanically (e.g., via sclerotherapy) or pharmacologically, can also lead to a decrease in LIC.

In patients with LIC or risk of LIC, there has been concern for new or worsened coagulopathy triggered by surgical or procedural interventions, resulting in treatment with perioperative anticoagulation. However, retrospective reports of pediatric patients with high- and low-risk VMs with and without LIC who undergo vascular interventions showed a low risk of bleeding or thrombosis, suggesting that periprocedural anticoagulation may not be warranted in most cases.[39]

Kasabach–Merritt Phenomenon

KMP is a serious coagulopathy that is seen in ~70% of infants with KHE or tufted angioma (TA),[40] two types of aggressive vascular tumors. KMP is characterized by moderate to severe thrombocytopenia, hypofibrinogenemia with elevated d-dimer, prolonged PT, prolonged aPTT, and occasionally microangiopathic hemolytic anemia. The risk of bleeding is high in these patients and carries with it a mortality rate of up to 30%; therefore, urgent identification of KMP and treatment is crucial to reduce the complications. Of note, the peripheral laboratory findings in KMP and LIC may resemble those seen in

DIC, with the distinction that they occur locally within the vascular anomaly. Chronic KMP and LIC when untreated, however, may progress to systemic DIC.[41]

While multiple pharmacologic agents have been reported to treat KMP, current treatment typically includes rapid initiation of both corticosteroids and sirolimus (even in neonates), with the addition of vincristine in severe or refractory cases. Supportive care with transfusions of cryoprecipitate for hypofibrinogenemia or packed red blood cells for anemia can be given as needed, but platelet transfusion to treat thrombocytopenia should be avoided unless there is active bleeding as it may worsen platelet trapping and consumptive coagulopathy after transfusion.[41,42] Antifibrinolytics have also been used for KMP to reduce the underlying hyperfibrinolysis, but the benefit is not clear and is typically not recommended unless used to treat active bleeding.

Propranolol for Infantile Hemangiomas

Infantile hemangiomas (IHs) are a common finding in up to 5% of infants.[43] In contrast to congenital hemangiomas that are fully developed at birth and do not experience a proliferative phase, IHs are not fully developed at birth and experience a rapid proliferative phase during the first 6 months of life. They then enter a dormant phase for 6 to 12 months, followed by slow and natural involution, such that up to 90% are resolved by the age of 9 years.[44]

Most IHs follow a benign clinical course and do not require medical treatment. In uncomplicated superficial IHs in which treatment is desired or in which systemic therapy is not tolerated, treatment with topical timolol maleate has been shown to be safe and effective in reducing the redness and volume of the IH.[45,46] In complicated IHs that ulcerate or bleeding, or cause mass effect and obstruction in the airway, nasal passages, orbit, or other vital structures, systemic therapy with propranolol is effective, well tolerated, and considered the standard of care in therapy.[1]

Propranolol acts as a nonselective β-adrenergic antagonist and its effect on IHs is theorized to be through feeding vessel vasoconstriction, inhibition of VEGF and vascular growth, and GLUT1 receptor blockade.[47] Propranolol has been shown to be as effective or more effective than prednisolone alone or in combination with prednisolone in clinical trials and is favored due to its lower side effect profile.[48,49] The FDA approved the first medication specifically for the treatment of IHs in pediatric patients in 2014 with the introduction of Hemangeol (propranolol hydrochloride, Pierre Fabre, France). In patients older than 5 weeks with no hypoglycemia or cardiopulmonary disease, Hemangeol is dosed at 1.2 mg/kg/day with escalation to 2.2 and then 3.4 mg/kg/day in two divided doses. Side effects occur in up to 8% of children and are usually mild and well tolerated when caregivers are appropriately counseled regarding dose escalation, feeding instructions, and appropriate use. More so, systemic propranolol can be safely initiated and used in the outpatient setting for patients without heart, lung, or glucose comorbidities.[50]

The ideal time to treat IHs is during the proliferative phase, which occurs during the first 6 to 8 months of life. Treatment is usually through the duration of the proliferative phase, then can be stopped around 12 months or life. Propranolol can be used at older ages, but there is often limited to no effect. When an IH does not improve with systemic propranolol therapy or continues to proliferate, one must consider adjunctive therapies such as corticosteroids, embolization, and/or surgery, in addition to reevaluation of the diagnosis with possible advanced imaging or histologic and tissue-specific genetic testing.

It is important to mention that while IHs can be found anywhere in the body, IHs in several specific locations are associated with other clinic findings that require further investigation and clinical considerations. First, large (>5 cm) segmental IHs in the head, neck, and upper extremity region can be associated with PHACE syndrome (**p**osterior fossa defects, **h**emangiomas, cerebrovascular **a**rterial anomalies, **c**ardiovascular anomalies, **e**ye anomalies). Of note, the initiation of propranolol can lead to transient hypotension; so, it is important to assess for the possible intracranial arteriopathy before starting propranolol to avoid the risk of stroke. Large (>5 cm) segmental IHs to the genitourinary region can be associated with LUMBAR syndrome (**l**ower body hemangioma, **u**rogenital anomalies and ulceration, **m**yelopathy, **b**ony deformities, **a**norectal malformations arterial anomalies, and **r**enal anomalies). An IH to the midline lumbosacral region can be associated with occult spinal dysraphism and warrants further screening.[51] Five or more cutaneous IHs warrant evaluation of the liver because they are associated with the presence of liver hemangiomas, which when large can be associated with hypothyroidism or cardiac failure.[52]

Corticosteroids for Hemangiomas and Other Vascular Anomalies

As mentioned, systemic corticosteroids have been shown to be effective in the treatment of IHs but, due to a higher side effect profile, are not preferred for first-line therapy. Corticosteroids are reserved for IHs in which systemic propranolol is not available, is contraindicated, or is not clinically tolerated due to side effects.

Congenital hemangiomas, as opposed to IHs, have not been shown to be responsive to any specific pharmacotherapies; so, therapy with topical or systemic propranolol is not indicated. There are reports of corticosteroid use being beneficial in some patients with hematologic abnormalities or those complicated by ulceration.

Corticosteroids can also be indicated and transiently used in patients with symptomatic KHE with or without KMP, TA, and in complex lymphatic anomalies with acute inflammation.

Conclusion

In the past, surgical and procedural interventions were the mainstay in the treatment of vascular anomalies, as pharmacotherapies were quite limited in the management of patients with these conditions. Fortunately, research over the past two decades has uncovered a deeper understanding of the molecular and genetic basis for vascular anomalies and

overgrowth syndromes, leading to the development and use of more targeted pharmacotherapies. This has given patients more multimodal treatment options and improved quality of life, which has made the treatment of these patients much more exciting and satisfying for healthcare providers. The future will see continued research that will lead to even more specific, potent, and effective pharmacotherapies, including novel drug-delivery mechanisms, which will continue to be incorporated into the multidisciplinary and holistic care of patients with vascular anomalies.

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