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REVIEW ARTICLE

Targeted treatments for vascular malformations: current state of the art

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Abstract

Vascular malformations, which arise from anomalies in angiogenesis, encompass capillary, lymphatic, venous, arteriovenous, and mixed malformations, each affecting specific vessel types. Historically, therapeutic options such as sclerotherapy and surgery have shown limited efficacy in complicated malformations. Most vascular malformations stem from hereditary or somatic mutations akin to oncogenic alterations, activating the PI3K-AKT-mTOR, RAS-MAPK-ERK, and G-protein coupled receptor pathways. Recognizing the parallels with oncogenic mutations, we emphasize the potential of targeted molecular inhibitors in the treatment of vascular malformations by repurposing anticancer drugs. This review delves into the recent development and future use of such agents for the management of slow- and fast-flow vascular malformations, including in more specific situations, such as prenatal treatment and the management of associated coagulopathies.

KEYWORDS
angiogenesis inhibitor, anticoagulation, sirolimus, targeted therapy, thalidomide

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1 | INTRODUCTION

Vascular malformations arise from defects during early vascular development, leading to the formation of abnormally structured vessels. They are categorized based on the affected vessels and flow velocity into slow-flow vascular malformations; encompassing venous (VMs), capillary, and lymphatic (LMs) malformations; and fast-flow vascular malformations, such as arteriovenous malformations (AVMs) [1]. Figure 1 summarizes the classification of vascular malformations on the basis of the current classification by the International Society for the Study of Vascular Anomalies (ISSVA) [1]. Representative clinical pictures are presented in Figure 2.

Most vascular malformations are congenital, present at birth, and expand during the patient's lifetime; however, novel lesions can also emerge over time. They can significantly impact the quality of life and their expansion induces chronic pain, deformities, functional limitations, infections, bleeding, and, in severe cases, death. Conventional treatments often yield unfavorable outcomes, especially for extensive vascular malformations for which procedures like sclerotherapy, embolization, or surgery are frequently unfeasible or incomplete [2].

The majority of vascular malformations occur sporadically, appearing as isolated anomalies primarily caused by somatic mutations that result in excessive activation of signaling pathways involved in angiogenesis. More rarely, vascular malformations are inherited, such as capillary malformation–AVM or multiple cutaneous and mucosal VM, and result from the combination of an inherited mutation and a second-hit mutation, resulting in complete localized loss of protein function that triggers the development of vascular lesions [3–5]. Vascular malformations and cancers share common pathogenic variants in signaling pathways, highlighting the possibility of repurposing anticancer medications in vascular anomalies.

2 | TARGETED THERAPY FOR SLOW-FLOW VASCULAR MALFORMATIONS

2.1 | Phosphoinositide 3-kinase–protein B–mammalian target of rapamycin pathway in slow-flow vascular malformations

VMs and LMs are prevalent within the spectrum of slow-flow vascular malformations. VMs usually manifest as single, soft, and compressible

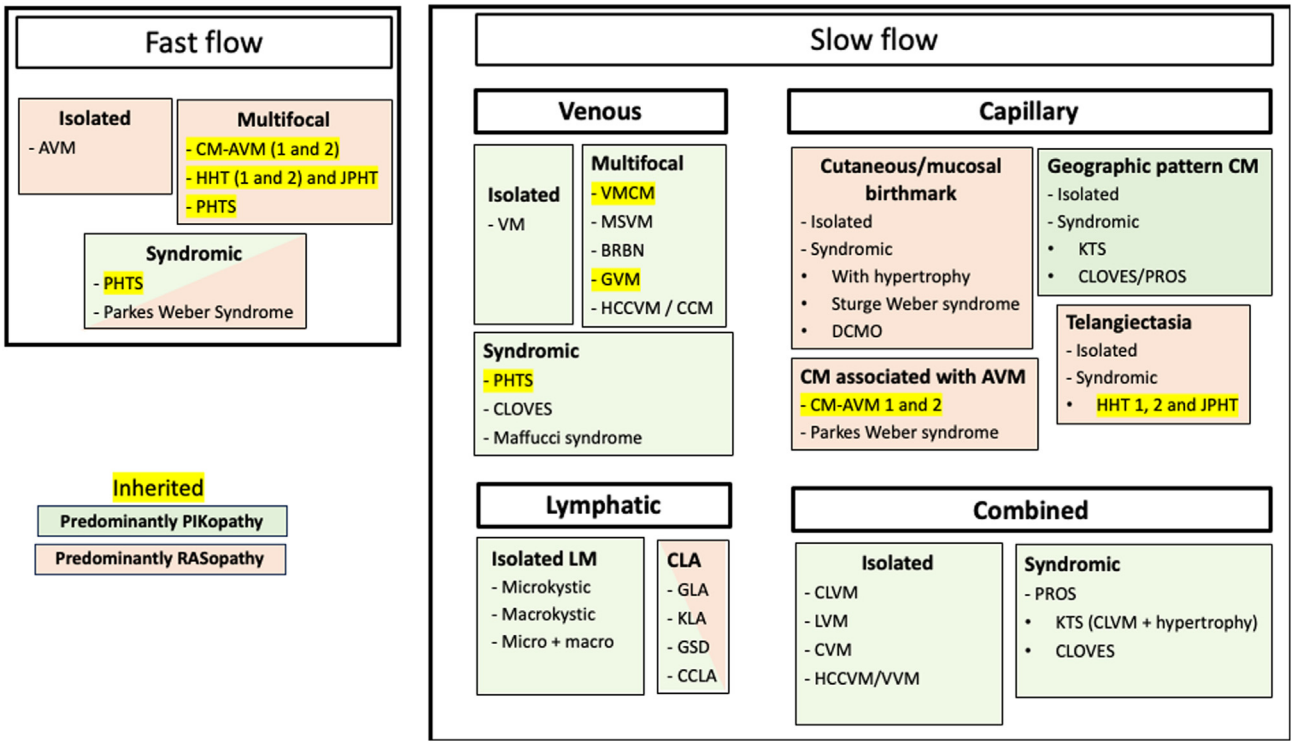

FIGURE 1 Classification of vascular malformations. AVM, arteriovenous malformation; BRBN, blue rubber bleb nevus syndrome; CCLA, central conducting lymphatic anomaly; CCM, cerebral cavernous malformation; CLA, complex lymphatic anomaly; CLOVES, congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis; CLVM, capillary-lymphatic-venous malformation; CM, capillary malformation; CM-AVM, capillary malformation–arteriovenous malformation; CVM, capillary-venous malformation; DCMO, diffuse capillary malformation with overgrowth; HCCVM, hyperkeratotic capillary–venous malformations; GLA, generalized lymphatic anomaly; GSD, Gorham–Stout disease; GVM, glomuvenous malformation; HHT, hereditary hemorrhagic telangiectasia; JPHT, juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; KLA, kaposiform lymphangiomatosis; KTS, Klippel–Trenaunay syndrome; LM, lymphatic malformation; LVM, lymphatic-venous malformation; MSVM, multifocal sporadic venous malformation; PHTS, PTEN hamartoma tumor syndrome; PROS, PIK3CA-related overgrowth spectrum; VMCM, cutaneomucosal venous malformation; VM, venous malformation, VVM, verrucous venous malformation.

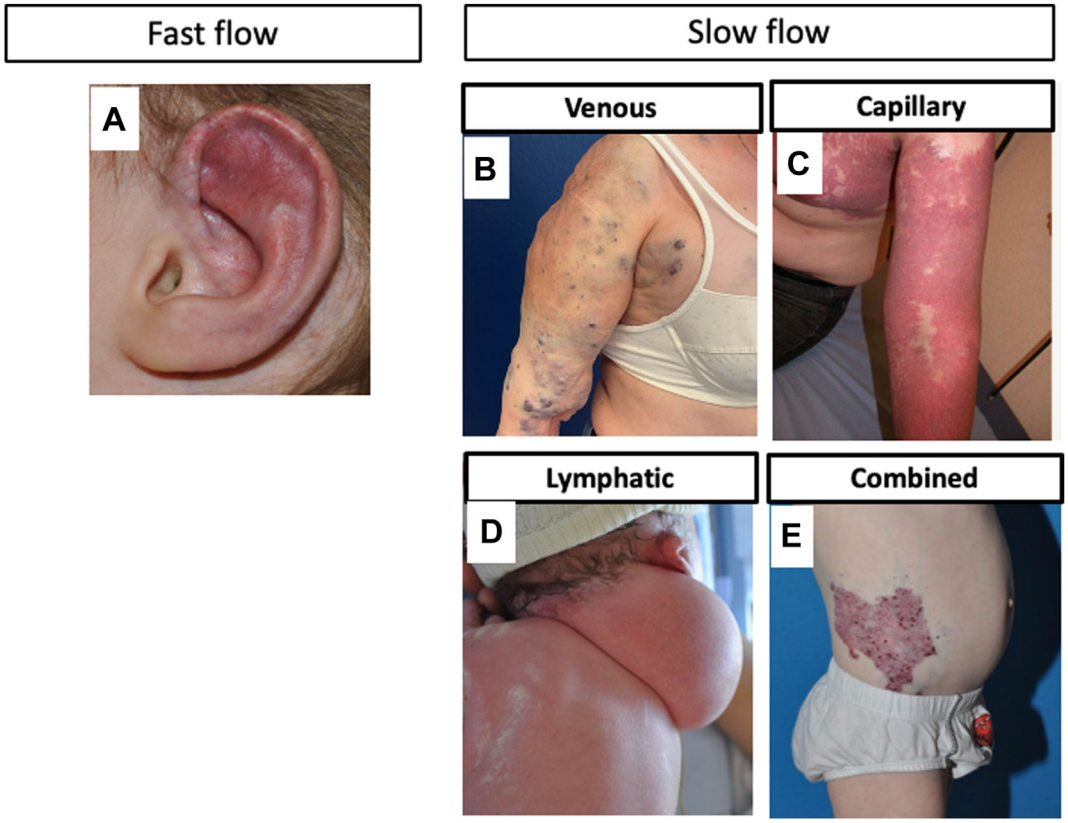

FIGURE 2 Representative pictures of vascular malformations. (A) Arteriovenous malformation of the ear. (B) Venous malformations of the arm with localized intravascular coagulopathy. (C) Capillary malformation of the arm. (D) Cervicofacial lymphatic (macrocystic) malformation. (E) Combined malformation, capillary-lymphatic-venous malformation.

lesions that vary in size from a few millimeters to several centimeters. They can affect any part of the body. Multiple VMs are also rarely observed in conditions such as multifocal VM, multiple cutaneous and mucosal VM, or blue rubber bleb nevus syndrome [6]. Histologically, VMs are characterized by enlarged and distorted vein-like channels, featuring a single layer of endothelial cells (ECs) enveloped by a disorganized extracellular matrix and smooth muscle cells.

LMs are subdivided into cystic LMs and complex lymphatic anomalies (CLAs). Cystic LMs occur as solitary lesions of variable size, and their structure defines them as macrocystic (large fluid-filled cavities) or microcystic (small cysts and diffuse vessel-like lesions). CLAs are much rarer, involve multiple localizations, and result in accumulation of fluid due to impairment of lymphatic function [7].

Combined malformations associate venous anomalies with other vascular defects, including capillary-venous, lymphatic-venous, or capillary-lymphatic-venous malformation (CLVM). Combined malformations may also be part of syndromes, including Klippel–Trenaunay syndrome (KTS; composed of a CLVM plus soft tissue and bony hypertrophy) or congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis (CLOVES) syndrome [8].

The majority of VMs arise due to gain-of-function somatic pathogenic variants within the tyrosine kinase with immunoglobulin and EGF homology domains (TIE2)–phosphoinositide 3-kinase (PI3K)–protein B (AKT)–mammalian target of rapamycin (mTOR) pathway [9]. Binding of angiopoietin-1 to TIE2 initiates the PI3K-AKT-mTOR cascade activation. Both AKT and mTORC1 stimulate cell proliferation, survival, migration, and angiogenesis. Importantly PTEN attenuates the PI3K-induced activation of AKT. Crosstalk exists between the mitogen-activated protein kinase (MAPK) and the PI3K-AKT-mTOR pathways. PI3K can be directly activated by RAS and mTOR indirectly by extracellular regulated kinase (ERK; Figure 3) [4,10–12].

The pathogenic variants in the *TEK* gene encoding the TIE2 receptor result in its ligand-independent activation. More than 20 different mutations have been described with the L914F mutation representing 60% of TIE2-mutated sporadic VMs [9,13–16]. Pathogenic variants in *PIK3CA*, the gene encoding the p110a catalytic subunit of PI3K, are observed in around 20% of VMs. More than 90% of *PIK3CA*-mutated VMs have pathogenic variants causing amino acid changes E542K, E545K, or H1047R, which are the frequently found hot spot variants in cancer. Non–hot spot pathogenic variants are more frequent in PIK3CA-related overgrowth spectrum (PROS) [17]. These *TIE2* and *PIK3CA* pathogenic variants result in excessive activation of AKT, which, through inhibition of Forkhead box O1 (FOXO1), leads to inappropriately low platelet-derived growth factor-β (PDGF-β) levels and subsequent sparse pericyte coverage

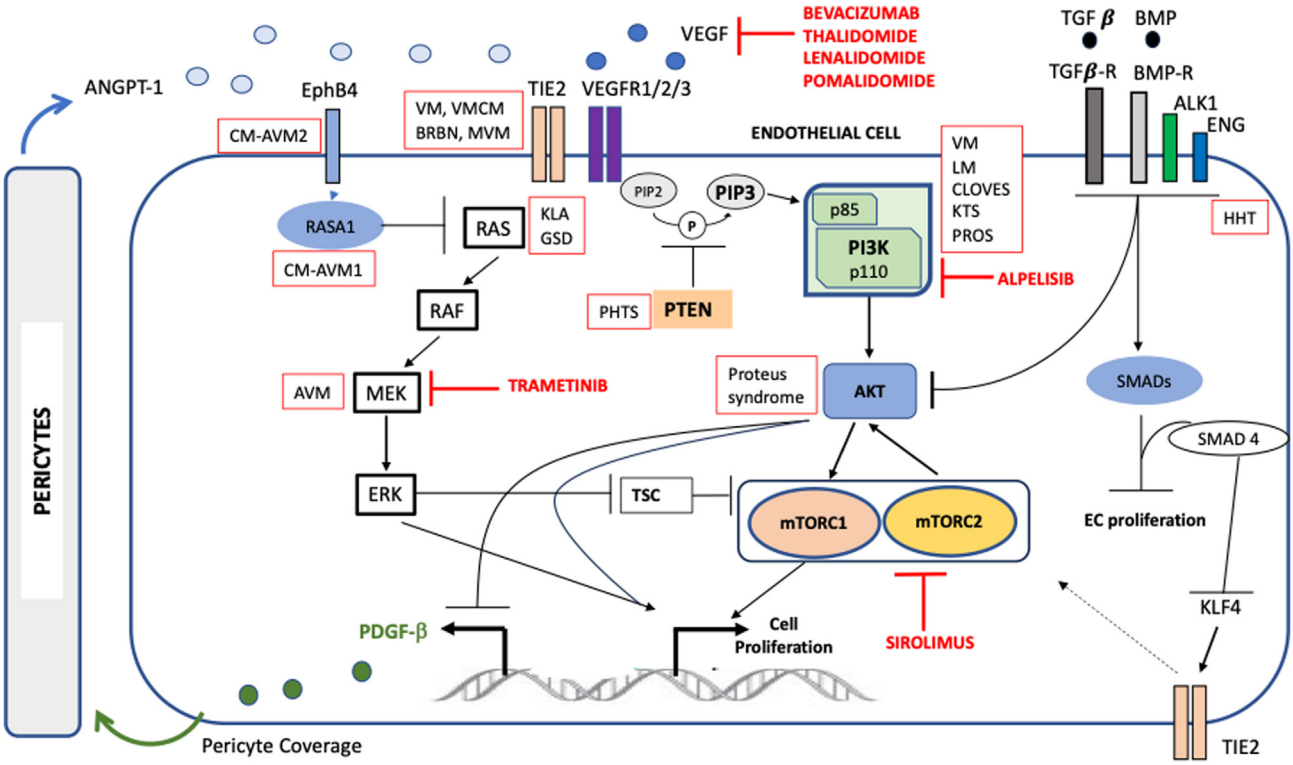

FIGURE 3 Vasculogenesis is regulated by important signaling pathways. Gain or loss of function mutations in genes of these pathways result in excessive activation of these cascades. Identification of these alterations allows repurposing of anticancer drugs in vascular malformations. AKT, protein kinase B; ALK, activin receptor-like kinase; ANGPT, angiopoietin; AVM, arteriovenous malformation; BMP (R), bone morphogenic protein (receptor); BRBN, blue rubber bleb nevus syndrome; CLOVES, congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis; CM, capillary malformation; CM-AVM, capillary malformation–arteriovenous malformation; EC, endothelial cell; ENG, Endoglin; EphB4, ephrin B4; ERK, extracellular regulated kinase; GSD, Gorham–Stout disease; HHT, hereditary hemorrhagic telangiectasia; KLA, Kaposiform lymphangiomatosis; KLF, Kruppel-like factor; KTS, Klippel–Trenaunay syndrome; LM, lymphatic malformation; mTOR, mammalian target of rapamycin; MVM, multifocal venous malformation; PDGF-β, platelet-derived growth factor-β; PHTS, PTEN hamartoma tumor syndrome; PROS, PIK3CA-related overgrowth spectrum; PTEN, phosphatase and tensin homolog; RASA, RAS p21 protein activator; SMAD, mothers against decapentaplegic homolog; TIE2, tyrosine kinase with immunoglobulin and EGF homology domains; TGF (R), tumor growth factor (receptor); TSC, tuberous sclerosis complex; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VM, venous malformation; VMCM, cutaneomucosal venous malformation.

[18]. Eighty percent of isolated and combined LMs also have 1 of the 3 hot spot pathogenic variants as seen in VMs [7,19]. The Table summarizes pathogenic backgrounds of vascular malformations.

2.2 | Preclinical testing and first clinical trials with sirolimus

The initial VM xenograft model using *TIE2-L914F* or H1047R *PIK3CA* mutated ECs demonstrated that sirolimus, an allosteric inhibitor of mTOR, effectively reduced VM growth and restored normal vascular tissue [18,20,21].

Based on these results, a pilot phase IIA trial evaluated sirolimus in 6 adult patients with highly symptomatic VMs (pain, bleeding, oozing, infection, and functional limitation) refractory to standard treatments. All patients experienced a decrease in symptoms and exhibited reduced D-dimer levels (most had chronic consumptive coagulopathy, also known as localized intravascular coagulopathy [LIC]) and an improvement in quality of life [18].

A subsequent phase IIB enrolled 19 patients (median age of 19 years, ranging from 9 to 64) with extensive slow-flow vascular malformation. They received sirolimus 2 mg/daily continuously (or 0.8 mg/m^2 twice daily for children) with a serum target concentration between 10 and 15 ng/mL. Sirolimus resulted in a 100% general improvement rate in terms of pain, functional limitation, bleeding, and oozing. When analyzing the 12-month follow-up magnetic resonance imaging, a size reduction was observed in 5 patients [22]. Another phase II trial, conducted by Adams et al. [23], reported similar results in 61 young patients with combined vascular anomalies, with an 82% rate of partial response.

The impact of sirolimus on volume reduction seems variable with vascular malformation subtypes. The phase II suPERficial Slow-flow Vascular malFORMations Treated With sirolimUS trial (PERFORMUS), which evaluated sirolimus in 59 children with a slow-flow vascular

TABLE Vascular malformations: molecular pathogenesis and suggested targeted therapy.

Location/association/ syndrome	Malformations	Mutated gene and typical mutation	Type of mutation (GOF vs LOF)	Target	Suggested treatment
Venous anomalies					
Isolated	Sporadic venous malformation	80% *TEK* (L914F) 20% *PIK3CA* (*E542-E545-H1047*)	Somatic GOF mutation	Direct activation of PI3K-AKT-mTOR	Sirolimus
Multifocal	Inherited cutaneomucosal venous malformation	*TEK* (R849W)	Germline GOF mutation (second-hit required)		
	Multifocal venous malformation	*TEK* (double mutation Y897C-R915C)	Mosaic GOF mutation (second-hit required)		
	Blue rubber bleb nevus syndrome	*TEK* (double mutations T1105N-T1106P and Y897F-R915L)	Somatic GOF mutation		
	Glomuvenous malformation	*Glomulin*	Germline LOF mutation (Second-Hit required)	Activation of PI3K downstream targets; inhibition of TGF-β signaling; increased protein ubiquitination	
Syndromic	Maffucci syndrome	*IDH1 (98%) or IDH2*	Somatic GOF mutation	Increase in oncometabolism	IDH inhibitor including ivosidenib (IDH 1)
Lymphatic anomalies					
Isolated	Cystic lymphatic malformation	80% *PIK3CA* (hotspot *E542-E545-H1047)*	Mosaic GOF mutation	Direct activation of PI3K-AKT-mTOR	Sirolimus
Complex lymphatic anomalies	Generalized Lymphatic anomaly	*55% PIK3CA* (hotspot *E542-E545-H1047)*	Mosaic GOF mutation	Direct activation of PI3K-AKT-mTOR	Sirolimus
	Gorham–Stout disease	*KRAS*	Mosaic GOF mutation	Direct activation of RAS-RAF-MEK	
	Kaposiform lymphangiomatosis	*NRAS*	Mosaic GOF mutation	Direct activation of RAS-RAF-MEK	Trametinib or other MEK inhibitor
		CBL	Mosaic LOF mutation	Activation of tyrosine kinase receptors	Consider addition of sirolimus
	Central conducting lymphatic anomaly	*EPHB4*	Germline LOF mutation	Decreased expression of *RASA1*	
Combined slow-flow malformations					
PIK3CA-related overgrowth syndrome	Klippel–Trenaunay syndrome	*PIK3CA* (mostly non–hot spot)		Direct activation of PI3K-AKT-mTOR	Alpelisib or sirolimus
	Congenital lipomatous overgrowth with vascular anomalies, epidermal nevi, and scoliosis	Mosaic GOF mutation			

(Continues)

TABLE (Continued)

Location/association/ syndrome	Malformations	Mutated gene and typical mutation	Type of mutation (GOF vs LOF)	Target	Suggested treatment
Capillary anomalies					
Isolated	Capillary malformation /Sturge–Weber syndrome	*GNAQ*, *GNA11*	Somatic GOF mutation	Activation of PLCβ and ERK	Trametinib or other MEK inhibitor to be considered
Association or multifocal	Capillary malformation–AVM 1	*RASA1*	Germline LOF mutation (second-hit required)	Increased expression of *RAS*	
	Capillary malformation–AVM	*EPHB4*	Germline LOF mutation	Decreased expression of *RASA1*	
Arteriovenous anomalies					
Isolated	Sporadic extracranial AVM	MAP2K1 *KRAS* *BRAF*	Somatic GOF mutation	Direct activation of RAS-RAF-MEK	Thalidomide Trametinib
Multifocal	HHT Juvenile polyposis HHT	*ENG*, *ALK1*, *HHT3*, *HHT4* *SMAD4*	Germline LOF mutation	Increased activity of PI3K and decreased activity of PTEN	Bevacizumab Thalidomide, Pomalidomide
AVM	PTEN hamartoma tumor syndrome	*PTEN*	Germline LOF mutation	Direct activation of PI3K-AKT-mTOR	Sirolimus

AKT, protein kinase B; ALK, activin receptor-like kinase; AVM, arteriovenous malformation; ERK, extracellular regulated kinase; GOF, gain-of-function; GNAQ, G protein subunit alpha Q; HHT, hereditary hemorrhagic telangiectasia; IDH, isocitrate dehydrogenase; LOF, loss of function; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RASA, RAS p21 protein activator; SMAD, mothers against decapentaplegic homolog; TGF, transforming growth factor.

malformation (37% VMs, 30% LMs, and 32% combined malformations) showed a statistically significant reduction in size only in patients with pure LM [24]. The impact of sirolimus on lesion size may be higher in children as suggested by the high reduction rate observed in a phase II trial that enrolled 126 children at early age (median age, 4.8 years); a ≥20% reduction was reached in 90% of VM and 84% of LM patients [25].

2.3 | The VASE trial confirms sirolimus

In 2016, we initiated the multicentric prospective phase III Vascular Anomaly-Sirolimus-Europe trial (VASE; EudraCT Number: 2015-001703-32) evaluating sirolimus in pediatric and adult patients with a slow-flow vascular malformation; 250 patients were enrolled. Recently, we shared preliminary results concerning 132 patients who either completed at least 12 months of follow-up after treatment initiation or prematurely arrested treatment [26]. The median age of the patients was 30 years (range, 0-73 years) and around 60% and 20% had VMs and LMs, respectively. These results unequivocally validated the efficacy of sirolimus in alleviating symptoms, with an impressive clinical improvement of 85% during the initial year of treatment; sirolimus reduced pain, improved functional limitation, and halted bleeding, oozing, and infection.

Sirolimus exhibited rapid effectiveness, with 74% of patients experiencing reduced pain within the first month. However, about 20% encountered an initial increase in pain or functional limitations within the first 3 months, some displaying transient rises in D-dimer levels akin to sclerotherapy-like mechanisms. Remarkably, sirolimus enabled further sclerotherapy or surgery for 14% of patients initially considered unsuitable for these treatments.

In the VASE trial, sirolimus was given for 2 years and then stopped. Among the 61 patients who completed the 2-year sirolimus course, only 36% needed to resume sirolimus, all experiencing subsequent clinical benefits; this suggests that sirolimus may not need to be administered indefinitely. Practically, based on this large prospective trial, sirolimus should not be interrupted too early as it may induce transient paradoxical increase in pain during the first 3 months. Sirolimus should be maintained for 1 to 2 years and then stopped. Correct imaging reevaluation should be done in order to assess feasibility of surgery/sclerotherapy. The patient should then be closely followed, and sirolimus should be reintroduced in case of emergence of moderate-to-severe symptoms [26].

2.4 | Toward a genome-based strategy

Although preliminary, our observations from VASE trial revealed similar rate of sirolimus efficacy in both *TIE2*- and *PIK3CA*-mutated patients. Interestingly, 67% of *PIK3CA*-mutated patients exhibited improvement within the first month, in contrast to only 26% of *TIE2*-mutated patients. In a similar way, the time to reach a worsening of the vascular malformation-related symptoms was shorter in *PIK3CA* mutation (all within the first 6 months) than in *TIE2* mutation (all after 9 months), suggesting that *PIK3CA* mutation may be associated with a sustained mTOR inhibition [26].

2.5 | Sirolimus and safety

While sirolimus is associated with adverse events (AEs) in most patients (96% in VASE trial), these are predominantly mild, easily manageable, and reversible, in line with other trials [18,22–27]. The most common grade 1-2 AEs observed in our phase II and III trials were asthenia (37%-70%), mucositis (37%-66%), diarrhea (37%-44%), headache (25%-58%), and cutaneous rash (31%-37%). Grade 3-4 AEs were reported in 18% of patients, including mostly mucositis (8%-11%); they resolved completely after dose adaptation or treatment cessation. Only 8% of patients had to definitively discontinue sirolimus due to AEs.

Like in the PERFORMUS trial, we did not observe any *Pneumocystis* infection, despite the absence of prophylaxis [24]. Notably, in the phase II trial conducted by Adams et al. [23], grade 3-4 bone marrow toxicity was reported in 28% of patients, a phenomenon that was not observed in any other trial. This could be attributed to the heavily pretreated, young and frail population enrolled in this specific trial. In our clinical practice, we consider *Pneumocystis* prophylaxis on a case-by-case basis, particularly for frail or very young patients with impaired pulmonary function and other comorbidities.

Sirolimus may impact fertility and perturb menstrual cycles, based on case reports and studies in solid organ transplant patients. Both male and female users may experience decreased fertility, but this normalizes after sirolimus discontinuation [28–31]. In the VASE trial, the incidence of dysmenorrhea was less than 10%, and it resolved in all cases after sirolimus arrest. During the follow-up of this trial, 2 females experienced 3 uncomplicated pregnancies within 3 years after sirolimus cessation, and a male became a father within 2 years after discontinuation, with all children developing normally [26]. These findings are reassuring and systemic sperm banking and/or ovocyte cryopreservation is currently not recommended.

In our clinical experience through the phase IIA, IIB, and III, 4 patients developed cancer during sirolimus treatment, including lymphangiosarcoma, a non–Epstein-Barr virus–related B-cell non-Hodgkin lymphoma, a pancreatic cancer, a breast cancer, and a nonmelanoma cutaneous tumor [18,22,26]. However, it is difficult to establish the responsibility of sirolimus considering: a) the rapid onset of cancer after sirolimus initiation (4 and 15 months); b) the anticancer properties of sirolimus in preclinical and clinical studies (including breast and pancreatic cancer) [32]; and c) the relatively low risk of sirolimus-related cancer compared with calcineurin inhibitor in graft-recipient patients [33]. While not minimizing the risk, we highlight the importance of closely following the patients who have been treated with sirolimus.

2.6 | More specific inhibitors targeting PI3K-AKT

Targeting PI3K emerges as another approach to manage vascular malformations, especially when associated with PROS. In a mouse model representing the PROS/CLOVES spectrum through mutant *PIK3CA* expression, the PI3K inhibitor alpelisib demonstrated superior efficacy over sirolimus in improving organ dysfunction and inducing vessel normalization. This preclinical success prompted a clinical study

involving 19 PROS patients. Alpelisib (daily starting dose of 250 mg for adults and 50 mg for children) consistently reduced the size of vascular lesions, improved congestive heart failure, and decreased hemihypertrophy. Alpelisib exhibited good tolerability, with transient hyperglycemia and mild mouth ulcerations in 2 and 3 patients, respectively [34].

The EPIK-P1 (NCT04285723) trial retrospectively reviewed efficacy of alpelisib in 32 patients with PROS. Twelve (37.5%) experienced a ≥20% reduction in target lesion volume at 6 months. Hyperglycemia (12.3%) and mucositis (10.5%) were the most common treatment-related AEs [35].

Recently, the efficacy of alpelisib was evaluated in 18 patients with vascular malformations, including 12 *TEK*-related and 4 *PIK3CA*-related VMs, 1 *TEK*-related veno-lymphatic malformation, and 1 *PIK3CA*-related AVM. Alpelisib improved the quality of life of all participants. In addition, alpelisib resulted in a greater reduction in radiological size in *PIK3CA*-related cases than in *TEK*-related cases (mean reduction of 53% vs 21%, respectively) [36]. However, unlike sirolimus, there is no long-term follow-up, particularly for fertility issues, as alpelisib is a novel drug. Furthermore, no prospective data have compared efficacy of alpelisib over sirolimus in PROS and *PIK3CA*-related slow-flow vascular malformation. Alpelisib may thus also be considered in patients who have failed to respond to sirolimus. Toxicity profile of alpelisib is different from sirolimus, with a higher rate of hair loss (up to 30%), diarrhea (up to 25%), hyperglycemia (up to 13%), and risk of growth retardation (up to 23%) in children, as recently presented by Paloma et al (oral presentation, ISSVA congress May 2024, Madrid). The MOSAIC study (NCT04316546) is an ongoing study evaluating miransertib, an allosteric AKT inhibitor, in patients with PROS and Proteus syndrome.

3 | TARGETING AT THE EARLIEST STAGE

We recently reported a successful *in utero* treatment of a fetal LM by sirolimus administered orally to the mother very early in the pregnancy, from 22nd week to 39th [37]. Even if close follow-up was initiated, the decision to start sirolimus was prompted by the rapid progression of the LM, leading to upper airway compression.

Adjustments to the daily dose ensured that the maternal serum level reached 10 to 15 ng/mL. Cordocentesis demonstrated that the fetal sirolimus level reached about 30% of the maternal sirolimus level. Only 1 week after achieving this maternal serum level range, the volume of LM decreased drastically. Importantly, no intrauterine growth restriction was observed, and the delivery was uncomplicated.

Postnatally, sirolimus was reintroduced shortly after birth due to rapid re-extension of the LM. At 15 months, sirolimus facilitated the surgical resection of the residual LM. This case stands out as a precursor, characterized by the exceptionally early administration of sirolimus and an extended follow-up period. The child, under a 6-year follow-up, has developed normally and is free from treatment. While this administration approach has since been adopted in some fetal intracardiac rhabdomyomas, there is only 1 additional reported case of fetal LM treated with sirolimus, initiated at the end of the third trimester [38,39].

4 | TARGETED THERAPIES IN AVM

4.1 | Targeting vascular endothelial growth factor in isolated AVMs

AVMs manifest as red cutaneous lesions which are often warm on palpation and with a detectable thrill. They are fast-flow anomalies, formed by abnormal connections between arteries and veins, bypassing the capillary network. AVMs can occur sporadically, with an estimated detection rate of 1.21/100 000 person-years; they typically exist since birth, are often solitary, can affect any tissue or organ, and progressively enlarge over time. Depending on their location, AVMs lead to structural deformities, pain, ulceration, anemia, and functional limitations. Common therapeutic approaches involve embolization followed by surgery, although remaining highly challenging and complex [40–42].

Animal models have highlighted the pivotal role of vascular endothelial growth factor (VEGF) in the pathogenesis of AVMs, with a clear association observed between VEGF levels and the severity of AVMs and complication rates in mice [43,44]. Clinical investigations revealed also increased VEGF expression in resected sporadic brain AVMs compared with normal brain tissue. Additionally, AVM patients exhibited elevated plasma VEGF levels in comparison with healthy controls. Furthermore, plasma levels of VEGF appeared to be more prevalent in incompletely embolized AVMs [45–47]. This suggests a potential link between invasive treatments and reactive angiogenesis.

Consistent with these findings, the monoclonal anti-VEGF antibody bevacizumab was shown to decrease vascular cell proliferation, vessel density, and dysplasia in mice with *ALK1*-induced brain AVMs [48]. However, clinical efficacy of bevacizumab has not been demonstrated; in a pilot study enrolling 2 AVM patients, bevacizumab did not induce any decrease in volume at 26 or 52 weeks. Thus, there is no role for bevacizumab in the standard management of AVM, outside clinical trials [49].

Thalidomide, by binding to cereblon, an E3 ligase adapter, recognizes VEGF and facilitates its degradation through the ubiquitin-proteasome pathway [50]. In addition to this antiangiogenic effect, thalidomide exerts an anti-inflammatory and immunomodulatory influence through inhibition of tumor necrosis factor-α and nitric oxide. In a mouse model of brain AVM, thalidomide and its derivative, lenalidomide, were shown to reduce hemorrhagic complications by increasing mural cell coverage of abnormal vessels [51].

We conducted a prospective clinical study assessing the efficacy of thalidomide in 18 patients with extensive, recurring, and highly symptomatic extracranial AVMs [52]. In the initial phase, the first 5

patients were administered a starting dose of 50 mg daily, progressively increased to 100 mg or 200 mg within 2 weeks. Remarkably, this cohort experienced significant and rapid pain reduction, complete cessation of bleeding, and healing of ulcerations within 1 to 2 months. Angiographic assessments unveiled AVM reduction in 1 patient after 6 months and complete disappearance in another one after 19 months.

Grade 3 AEs in 4 patients (asthenia, erythroderma, and a small cerebral infarct) led to the use of a lower dose (50 mg) for the 13 subsequent patients, still resulting in clinical improvement. After thalidomide discontinuation, symptom-free periods persisted for 13 and 10 months in the high-dose and low-dose groups, respectively. Thalidomide, used alongside embolization, showed potential for extended recurrence-free intervals, which may be explained by the prevention of the secondary VEGF release induced by surgery or embolization [53,54].

Peripheral neuropathy is a dose- and time-dependent AE of thalidomide, leading to axonal injury and the depletion of large-diameter myelinated nerve fibers. A neurological assessment, including clinical evaluation and a 2-point discrimination test, is essential before starting thalidomide to identify patients susceptible to peripheral neuropathy. Distal limb numbness, dysesthesia, muscle weakness, hypotonia, and declining tendon reflexes must be closely followed during thalidomide therapy. Prompt withdrawal of thalidomide upon detecting these symptoms is crucial to prevent irreversible neurological damage [55].

4.2 | Targeting VEGF in hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia characterized by the presence of multiple small mucosal telangiectasia and AVMs, commonly located in the lungs, liver, and/or brain. Even if the incidence of HHT may be as high as 1 to 2 in 10 000, not all HHT patients have AVM. HHT is caused by mutations in genes involved in transforming growth factor-β signaling and angiogenesis, such as *endoglin* and *activin-like-kinase 1*, and the intracellular transcription factor: *SMAD-related protein 4* [4]. Loss of function in these genes enhances EC migration, proliferation, and vessel formation. Multiple reports and studies showed that bevacizumab decreased severity of epistaxis, need for transfusions and improved secondary cardiac insufficiency in HHT [56–59].

The French HHT Network assessed bevacizumab efficacy in 25 HHT patients with severe liver involvement and high cardiac index. Bevacizumab (5 mg/kg every 14 days for 6 injections) elicited a response in 20 of 24 evaluable patients, with 3 achieving normalized cardiac index. Benefits were seen at 3 months and sustained for 6 months, with a significant reduction in mean epistaxis duration [60]. Optimal duration remains uncertain. In the retrospective "InHIBIT-Bleed study" involving 238 HHT patients, continuous administration of bevacizumab showed more efficiency compared with intermittent use. The most frequent reported AEs included infections (up to 22%), arterial hypertension (11%-18%), fatigue (10%), rheumatologic symptoms (6%-11%) and proteinuria (9%) [61]. Based on these observations, bevacizumab received a positive orphan drug designation status for HTT treatment in 2014 (EU/3/14/1390). Based on promising results in a small trial [62], ongoing larger trials are evaluating the efficacy of the tyrosine kinase inhibitors pazopanib (NCT03850730) and nintedanib (NCT03954782) in HHT.

Preclinical studies showed that thalidomide enhances PDGF-β expression and mural cell coverage in ECs in mice heterozygous for a null mutation in *endoglin* [63]. In a phase II trial, thalidomide was evaluated in 31 HHT patients with severe recurrent epistaxis. Starting at 50 mg/d orally, doses were escalated by 50 mg increments every 4 weeks until response, reaching a maximum of 200 mg/d. Improvement in epistaxis severity was observed in all patients, with 81% showing response at 50 mg/d, indicating efficacy at low doses. Thalidomide tolerability was generally favorable, with manageable mild AEs including asthenia, peripheral edema, constipation, dizziness, and neuropathy [64]. In 2017, thalidomide received positive orphan drug status designation for HHT.

Pomalidomide, an analog of thalidomide, seems promising for the management of HHT. The clinical trial Pomalidomide for Treatment of HHT (PATH-HHT; NCT: 03910244) randomized 144 patients to receive pomalidomide (n = 95) or placebo (n = 49). Pomalidomide significantly reduced baseline epistaxis severity compared with placebo and improved HHT-specific quality of life score compared with placebo. Pomalidomide was associated with mild to moderate neutropenia (45%), constipation/diarrhea (60%), and rash (36%). Another trial is currently ongoing in order to evaluate 2 doses of VAD044, an AKT1 inhibitor 1 in patients with HHT (NCT05406362).

4.3 | Targeting the MAPK pathway in AVMs

The overactivation of the RAS-RAF-MEK cascade has emerged as a pivotal player in the pathogenesis of AVMs. This cascade starts with the activation of the protein kinase RAS by the EPHB4 receptor; this triggers the phosphorylation of RAF, which in turn phosphorylates MAP-extracellular signal-regulated kinase 1 (MEK1). This process results in the phosphorylation and translocation of the ERK1 and ERK2 into the nucleus where it activates various transcription factors.

Somatic pathogenic variants in *MAP2K1*, the gene encoding MEK1, have been identified in 70% of patients in a series of extracranial AVMs [65]. Other MAPK alterations, including activating pathogenic variants in *KRAS* and *BRAF*, have also been reported in brain AVMs [66]. Mouse models, wherein K-RAS activation was induced within vascular ECs, demonstrated the generation of vascular lesions in diverse soft tissues, including the brain, liver, and heart, reinforcing the role of the MAPK cascade in AVM development.

The MEK inhibitor trametinib exhibited promising efficaciousness in preclinical AVM models, normalizing vessel sizes and morphology [67]. Preliminary results from the monocentric TRAmetinib in Arteriovenous Malformation trial (TRAMAV), presented by Coulie et al. at ISSVA 2022 (EudraCT: 2019-003573-26), underscored trametinib

efficacy in 10 patients with extracerebral AVMs. Trametinib resulted in acneiform rash in all patients (grade 1-2 and grade 3 in 8 and 2 patients, respectively), highlighting the importance of progressively increasing the dose and considering prevention/early treatment with isotretinoin. However, strategic adjustments to the daily dosage significantly improved patient symptoms, including bleeding, pain, and ulceration (Coulie et al., Phase II TRAMAV trial in AVM, Oral presentation, ISSVA congress 2022, Vancouver). These findings highlight the potential of targeting RAS-RAF-MEK cascade in AVMs.

5 | TARGETED THERAPIES IN CLAS

Excessive activation of MAPK has also been reported in CLAs, a heterogeneous group of multifocal lymphatic disorders, in which LMs develop in different organs including the bones, often associated with central conducting lymphatic anomalies (CCLA). Currently, CLAs encompass different phenotypic subtypes that can be related to specific mutations; for example, N-RAS mutations have been reported in generalized lymphatic anomaly, K-RAS mutations in Gorham–Stout disease, A-RAF mutations in CCLA, and N-RAS mutations in patients with kaposiform lymphangiomatosis [68,69]. Mosaic activating K-RAS pathogenic variants were identified as culprits behind CCLA and lymphedema and notably highlighted the various clinical manifestations that may be associated [70].

Some animal models have been developed, using patient-derived cells, and showed that trametinib was able to block ERK phosphorylation in lymphatic ECs [71]. Different case reports have shown efficacy of trametinib in alleviating symptoms in some CLA patients [72]. Seront et al. [73] showed that combining a low dose of sirolimus and trametinib was superior to each of these drugs given separately in a patient with generalized lymphatic anomaly, reflecting the crosstalk between these 2 pathways.

6 | CONTROLLING COAGULOPATHY IN VASCULAR ANOMALIES

6.1 | Coagulopathy in VM and its management

Nearly half of VMs are associated with chronic consumptive coagulopathy, also known as LIC. Clinically, LIC may be asymptomatic or may be associated with painful thrombotic episodes. This coagulopathy is marked by elevated D-dimers and in severe cases by concomitant low fibrinogen levels and low platelet count [74,75]. D-dimer levels are >0.5 μg/mL in 42% to 58% of VM patients, with 25% to 39% of patients having levels superior to 1 μg/mL. The latter was associated with extended surface area, deep and/or muscle involvement, phleboliths, and localization on extremities [74,76–78].

D-dimer measurement is thus a helpful diagnostic tool. In the absence of another cause, elevated D-dimer levels are associated with a venous component in 96.5% of cases, including not only pure VM but also capillary-venous malformation and combined CLVM with overgrowth. By contrast, D-dimer levels are within the normal range in glomuvenous malformations, LMs, Maffucci syndrome, Parkes Weber syndrome, and AVMs. D-dimer level can also be normal in small, solitary VMs but is always elevated in multifocal small VMs pathophysiologically related to a *TIE2* alteration [74].

A severe complication of LIC is the aggravation into disseminated intravascular coagulopathy (DIC), defined as a widespread hypercoagulable state that can lead to both microvascular and macrovascular clotting and compromised blood flow, ultimately resulting in multiple organ dysfunction syndrome. This can occur in the context of sepsis, trauma, fractures, or pregnancy [74,76]. Patients with very high D-dimer levels (with concomitant low fibrinogen level) and visceral or joint VMs pose the highest risk of LIC progression to DIC. Surgical excision and sclerotherapy can, in this situation, lead to dramatic bleeding and DIC [74,77–82].

Local activation of coagulation can induce thrombotic events of variable size, due to fibrin deposit and clot formation [83]. In the context of extensive VM, history or current signs of thrombotic events were reported in up to 50% of patients [84]. Persistent embryonic veins such as vein of Servelle, characterized by ectatic veins without competent valves, in patients with KTS or CLOVES syndrome, carry a 2.5 to 4 times higher risk of thrombotic complications compared with patients affected with combined slow-flow malformations without abnormal embryonic veins [85].

Compression therapy is recommended whenever feasible. Antiplatelet agents, such as aspirin, have a limited effect on coagulopathy. Low-molecular-weight heparin (LMWH) indirectly inhibits both factors Xa and IIa via potentiation of antithrombin. In a prospective study, 20-day course of enoxaparin 100 anti-Xa units/kg once daily was efficient in rapidly reducing pain episodes in 22 VM patients with LIC-related pain, with a significant decrease in D-dimers and a trend in normalization of fibrinogen levels [74].

Surgery and sclerotherapy have been reported to aggravate LIC by direct activation of the coagulation cascade by EC damage and release of tissue factor. Even if no universal guidelines exist, it is commonly accepted that patients with risk of LIC aggravation or with active LIC should be considered for preoperative and postoperative LMWH to prevent/stop the consumptive process and restore normal fibrinogen levels and platelet counts perioperatively [81,86]. Our current strategy is described in Figure 4. Antithrombotic modality, of course, has to be discussed with hematologists who are familiar with the management of vascular malformations. Postoperative anticoagulation should also be considered in patients with persistent embryonic veins and/or venous ectasias, particularly of the lower extremities given the increased risk for venous thromboembolic disease [87].

Direct oral anticoagulants (DOACs) are an attractive treatment for long-standing anticoagulation, including dabigatran, which targets thrombin, and rivaroxaban, apixaban, and edoxaban, which target factor Xa. These drugs block major procoagulation pathways reducing thrombin and fibrin formation. Despite a lack of prospective trials and long-term follow-up, DOACs seem to demonstrate a safety and efficacy profile in patients with VM associated with coagulation

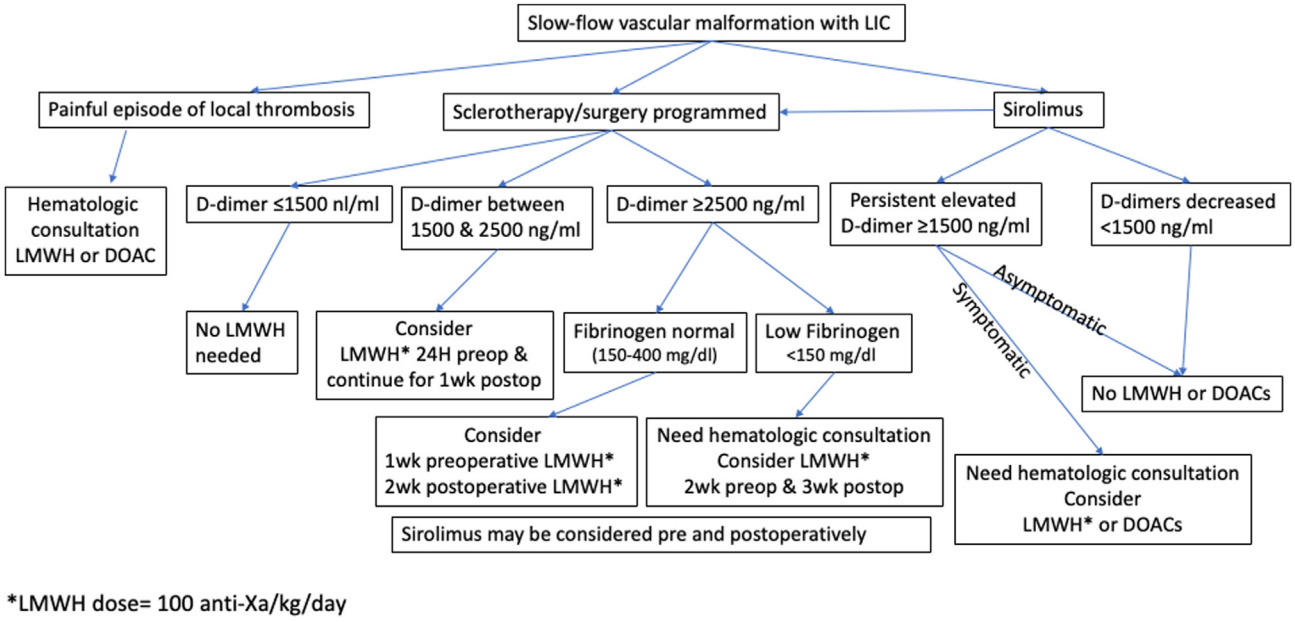

FIGURE 4 Our current therapeutic algorithm in the management of vascular malformations. DOAC, direct oral anticoagulant; LIC, localized intravascular coagulopathy; LMWH, low-molecular-weight heparin.

anomalies. Multiple reports have shown that dabigatran, rivaroxaban and apixaban were able to improve coagulation parameters (decrease in D-dimer and increase in fibrinogen levels) and alleviate pain in VM patients with LIC. As expected, they did not result in lesion regression, appearance change, or improvement in mobility [88–93]. In a retrospective study enrolling 29 patients with VM and LIC-related pain, DOACs improved pain in 85% of patients and reduced D-dimer by at least 25% in 86% of patients. Even if 10 patients (37%) experienced a bleeding episode, these events were minor (epistaxis, menorrhagia, gingival bleeding) and 4 were hematochezia related to the anorectal location of the vascular malformation [94].

The different DOACs have not been compared with each other. However, a retrospective analysis of 14 patients with KTS treated with DOAC (dabigatran, rivaroxaban, and apixaban) showed similar efficacy in preventing recurrence of deep venous thrombosis and reducing pain [95].

Sirolimus, by halting VM progression, may control coagulopathy, as observed by decreased D-dimer levels in the different trials [18,22,96]. In our current practice, we recommend starting sirolimus in patients with a slow-flow vascular malformation and LIC and to closely follow the D-dimer levels. LMWH or DOAC may be considered in case of persistent symptomatic LIC (which may reflect a noncontrolled disease; Figure 4).

6.2 | Targeted therapies-related coagulopathy

By targeting VEGF, bevacizumab and thalidomide were associated with increased number of bleeding or thrombotic events in cancer studies. In vascular malformation field, this association seems less clear. The incidence of thrombotic events with bevacizumab was very low in clinical trials enrolling patients with HHT. In a cohort of 69 HHT patients treated with bevacizumab for a mean duration of 11 months, there was no venous thrombotic event and only 1 arterial thrombotic event [97]; in the InHIBIT-Bleed study, the incidence was less than 2%. The incidence of venous thrombotic events related to thalidomide does not seem to be significantly increased either [61]. In a safety follow-up of 67 patients receiving thalidomide for a mean duration of 13 months, no venous thrombotic event was reported, suggesting that the risk is low [97].

Considering bleeding events, 2 cases have been reported with bevacizumab (1 grade 3 gastrointestinal bleeding and 1 fatal pulmonary hemorrhage in a patient with a large pulmonary AVM) and 1 case of fatal nose bleeding occurring in 1 patient treated with thalidomide [97]. Thus, caution should be paid in patients treated with bevacizumab or thalidomide, both for thrombotic or bleeding, particularly in patients with important risk factors or personal history of thrombotic events.

7 | CONCLUSIONS

Targeted therapies hold promise for enhancing outcomes for patients with vascular malformations. Future studies should focus on identifying clinical and genomic predictors of treatment response, optimizing timing and combination with other therapeutic modalities such as antithrombotic agents.

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AUTHOR CONTRIBUTIONS

E.S.: conceptualization, draft preparation, writing, review, and editing. C.H.: writing, review, and editing. L.M.B.: conceptualization, draft

preparation, writing, review, and editing. M.V.: conceptualization, draft preparation, writing, review, editing, and supervision.

ETHICS STATEMENT

Ethical approval was not required.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

DATA AVAILABILITY STATEMENT

Not applicable as no new unpublished data were generated for this review.

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