

REVIEW ARTICLE

Potential therapeutic targets and medications for arteriovenous malformations of the central nervous system

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Abstract

Arteriovenous malformations (AVMs) of the central nervous system are high-flow arteriovenous shunts that lead to considerable risks of hemorrhagic stroke and neurological deficits in young patients. Due to the complex angioarchitecture and their close anatomical relationship with the brain and spinal cord, the management of brain and spinal AVMs is challenging. Conventional invasive treatments, including microsurgery, endovascular embolization, and stereotactic radiosurgery, are associated with considerable risks and unsatisfactory efficacy. In addition, the lack of medications for AVMs represents an unmet clinical need. In recent years, the pathogenesis of AVMs has been progressively explored. The increased understanding of the mechanisms of the formation, progression, and rupture of AVMs has opened up several potential directions for AVM pharmacotherapy. In recent years, some promising drugs targeting angiogenesis, inflammation, vessel wall integrity, and the mitogen-activated protein kinase (MAPK)-extracellular receptor kinase (ERK) signaling pathway have been tested in a series of clinical investigations. In this review, we summarize the potential mechanisms, preliminary efficacy, and side effects of the candidate medications, including bevacizumab, minocycline or doxycycline, thalidomide, and trametinib, in the treatment of brain and spinal AVMs.

Keywords: Arteriovenous malformations; Therapeutic targets; Medication; Vascular integrity; Somatic mutations

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1. Introduction

Arteriovenous malformations (AVMs) are high-flow angiopathies that are characterized by direct connections between arteries and veins^[1]. Although AVM lesions have been detected in most bodily tissues, they are 20 times more likely to occur in the central nervous system (CNS), as with brain arteriovenous malformations (BAVMs) and spinal cord arteriovenous malformations (SAVMs), than in other locations^[2]. Nearly 95% of cases of AVMs in the CNS are sporadic or single lesions, while the remaining cases are genetic AVM syndromes, such as hereditary hemorrhagic telangiectasia (HHT), capillary malformation-arteriovenous malformation (CM-AVM) syndrome, and neurofibromatosis^[3,4].

BAVMs have an incidence of 1.3/100,000 patient-years, while the incidence of SAVMs has been reported to be 1/10th that of BAVMs^[5]. These lesions are a significant cause of hemorrhagic stroke in young patients. Natural history studies have shown that the annual hemorrhagic rate of an unselected BAVM cohort is 1%–4% and approximately 5% for patients with a rupture history^[6–11]. Considering that BAVMs are commonly observed in young patients aged 20 – 40 years, patients with BAVMs may harbor a significantly higher mortality risk than healthy populations^[12]. Compared to BAVMs, SAVMs are characterized by a greater clinical risk^[13]. They usually lead to neurological deficits, resulting from hemorrhage and venous hypertension of the spinal cord. The average age of onset of SAVM is 25 years, and its pre-treatment annual neurological deficit deterioration rate is over 30%^[13]. The largest cohort study has shown that the annual hemorrhagic rate is 10% and the cumulative spinal hemorrhagic rate 4 years after the initial onset of symptoms is 32%^[13].

Several interventional approaches, including microsurgery, endovascular embolization, and stereotactic radiotherapy, are used alone or in combination to obliterate AVM lesions. However, due to their complex angioarchitecture and their close anatomical relationship with brain or spinal cord tissue, the outcomes of current treatment strategies are unsatisfactory. It has been indicated that the complete obliteration rate in published BAVM cases was <50%, with a permanent treatment-related neurological deficit rate of 4 – 7%^[14,15]. The invasive interventions for SAVMs are even more challenging; the permanent treatment-related clinical deterioration rate reported in literature varies between 4% and 25%^[13,16,17], and <40% of patients can be cured. In addition, prospective clinical trials, such as a randomized trial of unruptured BAVMs (ARUBA), have shown that interventional therapy increases the risk of stroke or death in patients with unruptured BAVMs^[6]. The lack of pharmacotherapy for AVMs represents a compelling unmet clinical need and has thus prompted a series of laboratory-based and clinical investigations in the past two decades. The aim of this review is to summarize the potential pharmacotherapy targets and their clinical outcomes in the treatment of AVMs of the central nervous system.

2. Targets and medications

2.1. Angiogenesis

Although the detailed molecular pathobiology of AVM formation and progression is unclear, the growth and enlargement of AVM lesions are inevitably associated with the proliferation of vessels^[18,19]. Therefore, it has been

widely recognized that angiogenesis plays a key role in AVM pathogenesis.

The process of angiogenesis is regulated by pro- and antiangiogenic factors, and an imbalance between them would drive the sprouting of endothelial cells and newly formed vasculature^[20,21]. Compelling studies have indicated that vascular endothelial growth factor (VEGF) is a vital and essential pro-angiogenic molecule that stimulates and regulates angiogenesis. The previous investigations have shown that patients with BAVMs have higher plasma VEGF levels and significantly elevated expression of VEGF and VEGF receptors^[22–24]. A series of animal model-based studies have confirmed that the elevation of VEGF is a prerequisite for AVM formation and the inhibition of this pathway can restrict AVM occurrence^[22–26]. Therefore, the VEGF signaling pathway is expected to be a promising target for AVM pharmacotherapy.

Bevacizumab, a humanized monoclonal VEGF antibody, has been shown to effectively restrict tumor growth through its antiangiogenic effect. It was approved by the Food and Drug Administration (FDA) for the treatment of several solid cancers^[27,28]. The preliminary clinical outcomes of patients with HHT who are treated with bevacizumab are seemingly promising^[29,30]. Published Phase 1 and Phase 2 clinical trials of bevacizumab did not show any convincing anti-epistaxis effect in HHT patients^[31,32]. In another study conducted by Olsen *et al.*, bevacizumab significantly reduced cardiac output and relieved heart failure in HHT patients with liver AVMs^[33]. In addition, preclinical studies have shown that this drug could reduce the number of dysplastic vessels, as indicated by a 54% reduction in the dysplasia index in a HHT-based BAVM mouse model^[34]. Pazopanib (Votrient), another VEGF inhibitor, shows a convincing anti-epistaxis effect in HHT patients^[35]. **Table 1** shows the different clinical studies of bevacizumab and pazopanib according to timeline.

The above favorable results have prompted the investigation of the use of bevacizumab to reduce the risk of hemorrhage in CNS AVMs. However, a recently published proof-of-concept pilot study of bevacizumab in BAVMs has shown a negative result^[36]. As the first clinical investigation to evaluate bevacizumab as a treatment for sporadic BAVMs, the study recruited two patients with large (Spetzler–Martin Grade IV/V) brain AVMs who denied a history of intracranial hemorrhage (ICH). The participants received 5 mg/kg of bevacizumab every 2 weeks for 12 weeks; however, the AVM volumes observed 26 and 52 weeks after the treatment did not change compared to the baseline. Although the symptoms were stable and the patients' serum VEGF levels reduced, the results were still discouraging.

Table 1. Clinical Study of VEGF Inhibition.

Medication	Target	Publication	Phase	Dosage	Duration	Number of cases	Objective	Result	Side effect
Bevacizumab	VEGF	Simonds <i>et al.</i> , 2009 ^[30]	-	100mg, once	Retreatment is performed when needed	19	Evaluate the effectiveness	Frequency and severity of bleeding was decreased	Not displayed
Bevacizumab	VEGF	Karnezis <i>et al.</i> , 2012 ^[29]	-	100mg, once to 8 times,	Different for each patient	19	Evaluate treatment response	effectively for epistaxis and effective and lasted for 12 months	Not displayed
Bevacizumab	VEGF	Dupuis-Girod <i>et al.</i> , 2014 ^[31]	1	12.5/25/50/75/100 mg, once	once	40	Investigate the tolerance, bioavailability and efficacy	This nasal spray left no detection in the serum, and shows no efficacy	No dose limiting toxicity within the dose range
Bevacizumab	VEGF	Dupuis-Girod <i>et al.</i> , 2016 ^[32]	2/3*	25/50/75 mg	3 times, for a total duration of 4 weeks	80	Evaluate the efficacy	Epistaxis duration has no significant difference	No severe Adverse events reported
Bevacizumab	VEGF	Olsen <i>et al.</i> , 2020 ^[33]	-	5 mg/kg of body weight	6 times, for a total duration of 3 months	2	Find out treatment result	Effective for symptoms from the liver AVMs	Vulnerable and flossy nails reported; itchy, dry skin and alopecia areata
Pazopanib	VEGF	Marie <i>et al.</i> , 2019 ^[35]	-	50mg daily	12 weeks	7	demonstrate efficacy and safety	Decrease in epistaxis duration, > 2 gm improvement in Hgb	Bronchitis and nausea; elevated alanine aminotransferase (considered severe)

*: Termination of Phase 3 study before its launching due to previous unbeneficial results on the recommendations of the monitoring committee,

-: Phase not mentioned in the article or belonging to any of them, ALT: Alanine aminotransferase, AVM: Arteriovenous malformation,

Hgb: Hemoglobin, VEGF: Vascular endothelial growth factor

Although earlier experience of bevacizumab in the treatment of encephaledema, as an adverse effect caused by radiation in patients with brain AVMs, showed nidus obliteration after the administration of the drug, the combination of Gamma Knife limited the evaluation of the efficacy of bevacizumab in terms of accuracy^[37].

In addition, the anti-VEGF effect of bevacizumab is toxic to endothelial cells, which may increase the hemorrhagic risk of AVMs, as reported by Tanvetyanon *et al.*, and the side effects of the drug, such as thrombotic events, severe hypertension, and cardiac failure, are also significant^[38].

2.2. Inflammation

Similar to angiogenesis, the vital role of inflammation in the progression of brain AVMs has been recognized ever since early pathological studies were performed^[39]. In both human and mouse AVM samples, an upregulation in the expression of a series of inflammatory factors was observed. Furthermore, the infiltration of monocytes and granulocytes was also observed in surgical AVM samples.

A recently published single-cell atlas of BAVMs has established the contribution of inflammatory processes to BAVM rupture^[40].

Among various inflammatory factors, matrix metalloproteinase-9 (MMP-9) is the most concerned molecule because its activation has been shown to be associated with vascular wall instability^[41,42]. The matrix metalloproteinase inhibitor doxycycline has been evaluated for abdominal aortic aneurysm treatment^[43]. Since the previous studies have shown that the expression of MMP-9 is significantly upregulated in BAVM samples, theoretically, the inhibition of MMP-9 may stabilize the vasculature of AVMs and reduce the hemorrhagic risk^[44].

The earliest clinical investigation of MMP-9 in AVMs was conducted by Hashimoto *et al.* in 2005^[22], in which 10 patients received doxycycline (100 mg, twice a day) for 1 week before BAVM resection and four patients received placebo. Compared to placebo-treated AVMs, doxycycline-treated AVMs showed a trend of reduced MMP-9 expression^[45]. In 2008, Frenzel *et al.* published the results of a pilot study of minocycline and doxycycline in the treatment

of BAVMs^[46]. Twelve BAVM patients were recruited and were treated with minocycline or doxycycline (200 mg/day) for up to 2 years. The results of their follow-up suggested that patients with BAVMs are able to tolerate minocycline and doxycycline well; however, their results failed to show any trend toward potential patient benefit because one BAVM ruptured during the treatment. In another study, Burrows *et al.* used marimastat, another MMP inhibitor, for the treatment of a young girl with multiple AVMs involving the upper extremities^[47]. Following the treatment with marimastat, the young girl experienced pain relief, and there was healing of bony destruction; however, newly formed AVMs were observed during the treatment. Therefore, although the rationale of anti-inflammation therapy is justified and commended, there has been no solid evidence showing that it may benefit patients with AVMs of the CNS. Table 2 shows different clinical studies of MMP inhibitors according to timeline.

2.3. Vascular integrity

The results of emerging studies have suggested that BAVM rupture is associated with a maldeveloped vascular wall structure^[48-50]. Compared with healthy cerebral vasculature, the BAVMs in both human and mouse models are characterized by abnormal vessels lacking mural cells (vascular smooth muscle cells and pericytes), which are similar to engorged and expanded capillaries^[49]. With insights into the physiological function of mural cells, the above pathological features of AVMs may represent impaired vascular integrity and a tendency for rupture. As expected, clinical pathological investigations have indicated that these thin-walled vessels are the source of microhemorrhage and subsequent inflammatory reaction,

which has been shown to be correlated with ICH in BAVMs^[51]. Therefore, the repair of vascular mural cells has been considered a potential treatment strategy for BAVMs in recent years^[49,50].

This hypothesis was mainly inspired by the efficacy of thalidomide for patients with HHT, as shown in a study where the platelet-derived growth factor-B/platelet-derived growth factor receptor (PDGF-B/PDGF-R) signaling pathway was upregulated and mural cells were recruited following thalidomide intervention in mice^[52]. A series of clinical investigations have confirmed that oral thalidomide could significantly protect against epistaxis and gastrointestinal hemorrhage caused by telangiectasias^[53,54]. From pathological and genetic points of view, telangiectasias and AVMs are distinct lesions. However, the key pathological feature of telangiectasia is also the expansion of capillaries with pericyte coverage reduction. The previous studies have revealed that thalidomide can enhance pericyte coverage in telangiectasia by enhancing the expression of PDGF-B in endothelial cells^[52]. The PDGF-B/PDGF-R signaling pathway plays a key role in recruiting mural cells. During angiogenesis, endothelial cell paracrine PDGF-B and its receptor PDGF-R are mainly expressed in the precursors of pericytes and vascular smooth muscle cells^[52]. Although no compelling studies have found an impairment of the PDGFB/PDGFR signaling pathway in sporadic AVMs, the above findings still indicate that thalidomide may be a promising candidate for the pharmacological treatment of brain and spinal AVMs. To the best of our knowledge, thalidomide has not been investigated in patients with brain or spinal AVMs. A major concern about the use of thalidomide in AVM patients is its rare and frequent toxicities, such as teratogenicity and peripheral neuropathy^[55]. In addition, a relapse of epistaxis

Table 2. Clinical Study of MMP Inhibitors.

Medication	Target	Publication	Phase	Dosage	Duration	Number of cases	Objective	Result	Side effect
Doxycycline	MMP-9	Hashimoto <i>et al.</i> , 2005 ^[22]	-	100 mg, twice a day	One week	14	Investigate doxycycline effect for MMP-9	decreased MMP-9 in AVM tissues	Not displayed
Minocycline Doxycycline	MMP-9	Frenzel <i>et al.</i> 2008 ^[46]	-	100 mg, twice a day	Two years	26	Evaluate feasibility	Similar adverse event rates were recorded	Dose-limiting intolerance occurred in 31% minocycline and 23% doxycycline patients
Marimastat Doxycycline	MMP	Burrows <i>et al.</i> , 2009 ^[47]	-	30-120 mg, 100 mg, daily	Several years	1	Case report of treatment effect	Pain relieved, and recurrence of symptoms appeared	No adverse effects
Doxycycline	MMP-9	Lindeman <i>et al.</i> , 2009 ^[43]	-	50/100/300 mg, daily	2 weeks	60	Evaluate vascular inflammation level	Short and selective inhibitory effect on inflammation was recorded	Not displayed

--: Phase not mentioned in the article or belonging to any of them, AVM: Arteriovenous malformation, MMP-9: Matrix metalloproteinase-9

Table 3. Clinical Study of Thalidomide.

Medication	Target	Publication	Phase	Dosage	Duration	Number of cases	Objective	Result	Side effect
Thalidomide	PDGF-B	Lebrin <i>et al.</i> , 2010 ^[52]	–	100 mg, once a day	One month	7	Report the drug effect	6/7 patients acquired a lower rate of epistaxis frequency	Minor side effects: mild constipation, loss of libido, drowsiness and lethargy
Thalidomide	VEGF	Ge <i>et al.</i> , 2011 ^[54]	–	100 mg, daily	4 months	55	Investigate the long-term efficacy and safety	Thalidomide group showed effective response; VEGF were significantly reduced	No severe side effects while mild side effects were common
Thalidomide	Controversial	Invernizzi <i>et al.</i> , 2015 ^[53]	2	50-200 mg, daily	8-12 additional weeks after response	31	Study efficacy and safety	All patients' epistaxis symptoms were decreased	non-serious effects, one patient died considering unrelated

–: Phase not mentioned in the article or belonging to any of them, PDGF-B: Platelet-derived growth factor-B, VEGF: Vascular endothelial growth factor

has been observed following a cessation of treatment with thalidomide in HTT patients^[52]; therefore, the potential antihemorrhagic efficacy of thalidomide for AVMs may be nullified with the withdrawal of the drug. Table 3 shows different clinical studies of thalidomide according to timeline.

2.4. Mutation of mitogen-activated protein kinase (MAPK) pathway genes

The hereditary mechanism and the causative genes of AVM syndromes, such as HHT and CM-AVM syndrome, have been extensively investigated. However, the genetic basis of sporadic AVMs was not discovered until 2017, when Couto *et al.* performed whole-exome sequencing on 10 extracranial AVM samples and found that 7 (70%) of them harbored mutations in *mitogen-activated protein kinase kinase 1 (MAP2K1)* in endothelial cells^[56]. The results were confirmed by droplet digital polymerase chain reaction (PCR)^[56]. In 2018, Nikolaev *et al.* demonstrated somatic activating *KRAS* mutations in BAVM samples and localized the mutant gene in endothelial cells^[57]. Through ultra-deep next-generation sequencing of a panel of 422 common tumor genes and droplet digital PCR, our group also demonstrated a high prevalence (87.1%) of *KRAS/BRAF* somatic mutations in sporadic brain and spinal AVMs^[58]. Since *Kirsten rat sarcoma viral oncogene homologue (KRAS)*, *proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homologue B (BRAF)*, and *MAP2K1* all belong to the MAPK signaling pathway, these studies have confirmed that there is genetic homogeneity in sporadic AVMs. Figure 1 presents the *KRAS/BRAF* signaling pathway and MEK1 (also known as MAP2K1) inhibitor in sporadic AVMs.

Two important animal model studies have answered the question of whether the somatic mutations in MAPK

pathway genes are the cause of AVM formation or the consequence of AVM progression^[59,60]. They have found that both heterozygous *KRAS* G12D mutation and the overexpression of *KRAS* G12V in cerebral endothelial cells can cause BAVM lesions in mice. More importantly, these studies have verified that the activation of ERK-MAPK signaling pathway, rather than phosphoinositide 3-kinase (PI3K)-MAPK, is the cause of AVM formation, and trametinib, an MAP2K1 inhibitor, can restrict the development and progression of AVM in animal models^[60]. Therefore, a genotype-guided targeted treatment for sporadic AVMs with activating mutations of ERK-MAPK pathway genes has been developed, and trametinib has been used to treat four patients with extracranial AVMs thus far^[61-64]. Although the outcomes in these studies were measured in a crude and relatively subjective manner, the results still indicated that trametinib is effective in reducing the size of and blood flow to AVM lesions. Table 4 shows different clinical studies of trametinib according to timeline.

Clinical trials of trametinib in patients with BAVMs or SAVMs have not been reported in literature. One limitation is that genotype-guided management relies on the availability of AVM samples; however, a biopsy of brain or spinal AVMs is risky and not feasible in most cases. As a countermeasure, cell-free DNA sequencing may be a promising strategy, although its sensitivity is currently not favorable. Cooke *et al.* have revealed the findings of an endovascular biopsy, using coils to collect endothelial cells of BAVMs^[65]. The biopsy was inventively designed and is practical for patients with refractory BAVM lesions.

The results of recent clinical and animal model studies have suggested that trametinib may be a promising

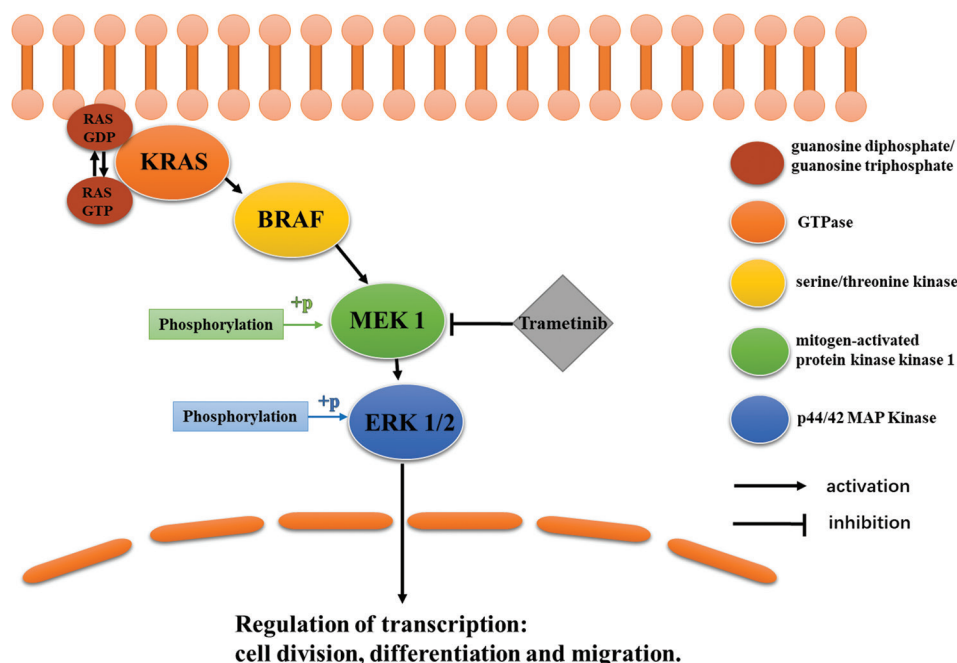


Figure 1. KRAS/BRAF signaling pathway and MEK1 inhibitor in sporadic arteriovenous malformations. Trametinib acts as a pathway inhibitor that blocks downstream responses.

Table 4. Clinical Study of Trametinib.

Medication	Target	Publication	Phase	Number of cases	Dosage	Duration	Objective	Result	Side effect
Trametinib	MEK inhibitor	Lekwuttikarn <i>et al.</i> , 2019 ^[63]	-	1	0.5mg, daily to twice a day	6 months	Report clinical effect	Found a reduced size and lighter color	A mild acneiform eruption
Trametinib	MEK inhibitor	Edwards <i>et al.</i> 2020 ^[61]	-	1	0.025 mg/kg, daily	6 months	Report clinical effect	75% reduction in arterial blood flow from the AVM	Not displayed
Trametinib	MEK inhibitor	Samkari <i>et al.</i> , 2021 ^[64]	-	1	Not mentioned	6 months	Report clinical effect	No more bleeding reported, found the AVM smaller and lighter in color	Not displayed
Trametinib	MEK inhibitor	Nicholson <i>et al.</i> , 2022 ^[62]	-	1	2.0-0.5mg, daily	Over a year, 0.5mg daily now	Report clinical effect	Shunting improved and AVM got more stable structures	Cutaneous toxicity

-: Phase not mentioned in the article or belonging to any of them, AVM: Arteriovenous malformation, MEK: Mitogen-activated protein kinase kinase

candidate for the treatment of brain and spinal AVMs^[60,66]. However, in a report of a patient with Cobb syndrome, we noticed that although the extracranial AVM had shrunk after trametinib treatment, the blood flow to and lesion size of the intracranial AVM had not changed^[61]. The concern about the sensitivity of brain and spinal AVMs to trametinib treatment is not groundless considering that AVMs of the CNS are quite stable compared with their extracranial counterparts^[67]. In addition, considering the longer survival rate of patients with AVMs than that of patients with malignant tumors, the side effects of antineoplastic drugs should not be neglected.

3. Perspectives and conclusion

Based on the understanding of the pathogenesis and pathophysiological mechanisms of AVMs, a series of drugs targeting angiogenesis, inflammation, vascular integrity, and MAPK-ERK pathway signaling have been assumed to be effective against the disease. Unfortunately, emerging evidence has revealed that the prospects of these drugs may not be as optimistic as expected. Bevacizumab used to be the most anticipated candidate; however, there was no change observed in the structure of BAVMs in patients who received the drug. MMP-9 inhibitors were thought to

be able to stabilize the vasculature of AVMs, but it has been reported that patients under MMP inhibition treatment still carry a risk for BAVM rupture. The use of thalidomide, on the other hand, may enhance the integrity of AVM vessels and reduce the hemorrhagic risk, but its noticeable toxicities undoubtedly restrict its use. In a patient with Cobb syndrome, trametinib has shown to be effective for the treatment of extracranial AVMs but not spinal cord AVMs, indicating that AVMs of the CNS may not be sensitive to trametinib, just as the natural course of brain and spinal AVMs is more stable than that of extracranial AVMs. The safety of trametinib should also be assessed for patients without malignant diseases. Although some of the findings have not been fully translated into clinical studies, they are still of interest. The Notch signaling pathway has been the subject of a number of research, some of which have revealed that it is activated in surgical specimens and its upregulation alters the vascular structure, as shown in a mouse model of Notch-mediated AVMs^[68,69]. The previous studies have also shown that members of the Notch signaling pathway and their downstream molecules are associated with angiogenesis^[70,71] and that hypoxia upregulates Notch signaling, thus causing inflammation and vascular remodeling^[72,73], whose subsequent reactions are related to the formation of AVM. Notch is associated with multiple pathways of conduction but its mechanism in AVM has not been fully elucidated^[74,75]. The study of Notch inhibitors is challenging due to their wide range of interactions. Unfortunately, clinical studies are not yet in sight. As of now, we know that Notch inhibitor causes dose-dependent inhibition of endothelial cell migration and network formation *in vitro*^[76]. A Smad family member 4 (Smad4)-inducible, endothelial cell-specific knockout (Smad4-iECKO) mouse model has established that angiotensin-2 inhibition rescues AVM formation, which is indeed an inspiring finding^[77].

We speculate that the relatively stable natural course of CNS AVMs compared to that of malignant tumors presents a challenge in the development of pharmacotherapy for AVMs. The evidence on the growth of AVMs in the brain or spinal cord is anecdotal, and the existence of arteriovenous shunts with expanded vascular caliber mainly relies on arterial blood flow rather than aberrant signaling pathways, as is the case with neoplasms. Therefore, pharmacotherapy strategies for malignant tumors may not be appropriate for AVMs. Given the applicability of the genetic-based mouse model of sporadic AVMs, we believe that further studies should be devoted to assessing the difference in expression between malformed vessels and intact vasculature. The development of specific markers may help distinguish AVM vessels from normal vessels, which may facilitate precise delivery of drugs for AVMs. In conclusion, invasive

treatments will likely continue to be the sole management strategy for AVMs for a considerable amount of time, and the lack of pharmacotherapy for brain and spinal AVMs represents an unmet clinical need and, without a doubt, a significant potential for innovative research.

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Conflict of interest

The authors declare that they have no competing interests.

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