Medical Adjuvants in the Treatment of Surgically Refractory Arteriovenous Malformations of the Head and Face: Case Report and Review of Literature

Vaidya Govindarajan Joshua D. Burks Evan M. Luther John W. Thompson
Robert M. Starke

Department of Neurological Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Keywords

Molecular target of rapamycin · Arteriovenous malformation · Rapamycin · Embolization · Adjuvant · Medical therapy · Vascular malformation · Surgery · Bleeding · Inoperable

Abstract

Background: Arteriovenous malformations (AVMs) of the brain and face present unique challenges for clinicians. Cerebral AVMs may induce hemorrhage or form aneurysms, while facial AVMs can cause significant disfigurement and pain. Moreover, facial AVMs often draw blood supply from arteries providing critical blood flow to other important structures of the head which may make them impossible to treat curatively. Medical adjuvants may be an important consideration in the management of these patients. **Summary:** We conducted a systematic review of the literature to identify other instances of molecular target of rapamycin (mTOR) inhibitors used as medical adjuvants for the treatment of cranial and facial AVMs. We also present 2 cases from our own institution where patients were treated with partial embolization, followed by adjuvant therapy with rapamycin. After screening a total of 75 articles, 7 were identified which described use of rapamycin in the treatment of inoperable cranial or facial AVM. In total, 21 cases were reviewed. The me-

dian treatment duration was 12 months (3–24.5 months), and the highest recorded dose was 3.5 mg/m². 76.2% of patients demonstrated at least a partial response to rapamycin therapy. In 2 patients treated at our institution, symptomatic and radiographic improvement were noted 6 months after initiation of therapy. **Key Messages:** Early results have been encouraging in a small number of patients with inoperable AVM of the head and face treated with mTOR inhibitors. Further study of medical adjuvants such as rapamycin may be worthwhile.

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Introduction

Arteriovenous malformations (AVMs) are a class of vascular anomalies characterized by a direct interface between arterial and venous blood supplies without an intervening capillary bed. AVMs are composed of 3 vascular structures: an aggregation of anomalous vessels (nidus), feeding artery or arteries, and a draining vein or veins [1]. While AVMs can occur in any organ, brain AVMs present unique challenges due to their tendency to induce hemorrhage, aneurysms, and venous ectasia [2]. Cutaneous AVMs have also been described in the literature and patients typically present with disfigurement,

pain, bleeding, and may experience complications such as thrombosis and organ dysfunction [3].

The current gold-standard treatment for brain AVMs involves microsurgical obliteration [4]. Other strategies, including embolization and radiosurgery, have yielded successful outcomes in appropriately selected cases [5]. Treatment of some AVMs, however, presents an unacceptable level of risk. This is particularly true of those which are deep, near critical structures, or too large [6]. Furthermore, some large-scale studies have demonstrated that partial embolization can increase annual bleeding rates [7], perhaps by increasing blood flow through the remaining blood supply. Additionally, if partially treated, an AVM may also recruit new supplying arteries.

While partial treatment of AVMs does not decrease risk of hemorrhage, some patients may still improve symptomatically from a reduction in shunted blood flow [24]. These patients present a significant challenge for clinicians, as they frequently require repeated embolizations over the course of their lifetime, sometimes multiple times per year. Given limitations of surgical and interventional techniques, there may be an important role for medical adjuvants in these cases.

Rapamycin, an inhibitor of the molecular target of rapamycin (mTOR), has been successfully implicated in the treatment of vascular diseases and has been shown to successfully treat lymphatic malformations, a related class of circulatory anomalies [8, 9, 23]. mTOR is a serine-threonine kinase that is a critical regulator of cellular proliferation and survival. Rapamycin exerts its effects by forming a complex with intracellular FK binding proteins (FKBP, specifically FKBP12), which directly inhibits mTOR, arresting the cell cycle at the G₁ phase and halting blood vessel formation [9, 10]. Treatment of AVM has been proposed as an off-label use of rapamycin given its mechanism of action and the potential for disrupting AVM pathophysiology. Furthermore, early results have been encouraging with treatment of pediatric AVMs of the head and face [3, 6]. In this article, we discuss 2 cases of patients recently treated at our institution with rapamycin and review available literature regarding medical therapy for inoperable AVM.

Methods

Literature Review

The study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We performed a systematic search of electronic databases, including PubMed, Cochrane, and Google Scholar, up to August 2020.

Keywords used in combination or individually were “arteriovenous malformation,” “AVM,” “coiling,” “facial,” “cranial,” “Rapamycin,” and “rapamycin,” using Boolean operators “OR” and “AND.” Search was also performed using “NOT”; “coronary,” “flow-diverting,” and “pipeline.” Articles identified in database search were then screened by title and abstract for eligibility. Those which passed screening were then downloaded and assessed against our inclusion criteria. Articles were reviewed by 3 authors independently, and articles were included by consensus. Further literature was examined by searching the reference lists of included studies.

Original research studies, case series, and case reports on patients placed on medical therapy for cranial or facial AVM were included. Exclusion criteria applied to studies containing only patients with AVMs in other parts of the body not including the head or face and studies on animals. Studies published in abstract form only, review articles, meta-analysis, guidelines, or lacking information on medications used were also excluded.

Treatments

Two patients with inoperable AVM of the head and face were treated at our institution after institutional review and approval (IRB #20190857). Our rapamycin protocol is as follows: when possible, patients initiate treatment 14–18 days prior to embolization, receiving 2 mg per day. Rapamycin concentrations are measured between days 4 and 7, following the initial rapamycin administration dosage. If rapamycin trough concentrations are low, then a loading dose may be considered in addition to the new maintenance dose. The loading dose is determined using the formula: Rapamycin loading dose = 3 × (new maintenance dose – current dose). Rapamycin trough concentrations were maintained within the therapeutic range of 3–20 ng/mL, and total treatment lasted 14–18 days.

Review of Literature

We identified 75 articles in our initial database search. All 75 records were screened, and 11 full-text articles were assessed for eligibility. Four articles were subsequently excluded. In 3 articles, the lesion site could not be identified, and one study was conducted in animals. We identified 7 studies that detailed treatment of head and face AVMs using rapamycin. From these studies, 21 patients were treated. The median treatment duration was 12 months (3–24.5 months), and the highest recorded dose was 3.5 mg/m². With regard to efficacy, 76.2% of previously treated AVM patients demonstrated at least a partial response to rapamycin therapy. A summary of previous reports on rapamycin use in cranial and facial AVM management is displayed in Table 1.

mTOR inhibitors are recently used alternatives to surgical management of large, superficial AVMs in the pediatric population, with rapamycin being the drug of choice in many published reports [3, 6]. To date, our study details the 22nd and 23rd known patients to be treated with an

Table 1. Summary of previous reports detailing the use of rapamycin in cranial or facial AVMs

Author	Objective	Dose	Methods	Response measure	Patients with facial or cranial lesions, <i>n</i>	Duration of treatment	Results
Dodds et al. [12]	Efficacy and tolerability of topical formulations of rapamycin in the treatment of various simple and combined vascular malformations and tumors	Topical rapamycin (17 used 1% rapamycin, 1 used 3% rapamycin)	Eighteen patients with any vascular anomaly treated exclusively with topical rapamycin were retrospectively reviewed	Response measured as therapeutic benefit in reduction of bleeding, infection, induration/thickness, blebs and exudate, pain, cosmesis, and functional impairment Clinicians rated therapeutic benefit as follows: 0% (none), 1–25% (minimal), 26–50% (moderate), or >50% (marked) improvement	1 patient with facial lesion	11 months	>50% reduction in induration/thickness
Hammer et al. [14]	To assess the efficacy and safety of this treatment in patients with extensive or complex slow-flow vascular malformations	2 mg/day (adults, children over 12) 0.8 mg/m ² /twice a day (children under 12)	Rapamycin was administered orally on a continuous dosing schedule	Response measured as follows: Complete resolution: complete disappearance of lesion or normalization of life quality Partial response: reduction of ≥20% in size of the vascular lesion, improvement of symptoms, or life quality Absence of response: Disease progression, disease stability, no improvement of symptoms, or life quality	4 patients with cranial or facial lesions	Average duration of 19 months for the remaining 4 patients	1 patient was not evaluable, 3 patients with demonstrated functional improvement
Gabeff et al. [13]	To evaluate efficacy of rapamycin in a series of 10 patients	0.6–3.5 mg/m ²	Retrospective analysis of patients treated with rapamycin	Response measured as follows Complete response: >90% decrease in AVM volume on clinical and imaging assessments Partial response: >25% decrease in AVM volume and/or healing of hemorrhage and necrosis No response: stabilization, <25% decrease in AVM volume or worsening	5 patients with facial AVM	Median treatment time was 24.5 months	2 patients nonresponsive, 3 patients with partial response
Maynard et al. [6]	Case report on pediatric patient with thalamic AVM	0.8 mg/m ²	Patient started on 1-year trial of rapamycin	Response defined as reduction in AVM volume on MRI and reduction in clinical symptoms (e.g., TIA frequency)	1 patient with cranial AVM	1 year	Patient currently responding well to treatment, >50% reduction in TIA frequency
Sandbank et al. [15]	19 patients treated with rapamycin for complicated vascular anomalies	Oral 0.6 mg/m ² rapamycin twice daily (17 patients) or application of 0.2% rapamycin gel (2 patients)	19 patients treated with rapamycin	Response measured as follows: Positive response: clinical/radiological stabilization or a decrease in lesion size, overgrowth, decreased thrombosis or cellulitis, improved life quality, or reduction in impairment or pain Partial response: improvement in the symptoms and a reduction in the lesion, but a persistence of the anomaly Complete response: resolution of symptoms and lesion	1 patient with cervicofacial lesion	3 months	Patient demonstrated partial response, reduction in lesion size

Table 1 (continued)

Author	Objective	Dose	Methods	Response measure	Patients with facial or cranial lesions, <i>n</i>	Duration of treatment	Results
Triana et al. [16]	Retrospective review of 41 patients treated with rapamycin for vascular lesions	0.8 mg/m ² /12 h	41 patients treated with rapamycin	Partial response: improvement of symptoms and reduction of the lesion, but persistence of the anomaly Complete response: disappearance of symptoms and lesion, without visualization of the anomaly by imaging	6 patients with cranial, facial, or cervicofacial lesions	8.5 months	Two patients did not respond to treatment, 4 patients did respond to treatment
Chelliah et al. [11]	Retrospective review of 6 patients treated with rapamycin	10–15 ng/mL target blood concentration	6 patients treated with rapamycin	Response: outcomes listed as decrease in AVM volume, resolution of pain and impairment, or bleeding. Measured on a case-by-case basis	3 patients with facial lesions	19 months	All 3 patients at least partially responded to rapamycin therapy

AVMs, arteriovenous malformations; TIA, transient ischemic attack; MRI, magnetic resonance imaging.

mTOR inhibitor for management of a cranial or facial AVM [6, 11–16]. There has been substantial variability in dosing and treatment duration across institutions, with treatment duration ranging from 3 to 24.5 months, with a median treatment duration of 12 months across all reported cases [17, 18]. With respect to dosage, all but 3 institutions dosed topical rapamycin treatment by surface area of administration, with the upper dosage limit being 3.5 mg/m² [17].

Determination of rapamycin response in the current literature is highly variable, with a mixture of parameters (reduction in lesion size, pain alleviation, bleeding episodes, etc.) being used to determine if a patient is nonresponsive, partially responsive, or fully responsive to rapamycin treatment [6, 15–19]. However, despite parameter variability, 16 of the 21 (76.2%) previously described patients in the literature demonstrated a favorable response to treatment. This promising level of efficacy is contrary to a recent systematic review of rapamycin usage in vascular malformations, which demonstrated only a low-level of evidence supporting rapamycin efficacy [17].

To date, there are only 2 randomized controlled trials investigating the role of mTOR inhibitors in vascular malformations, and none demonstrating the utility of rapamycin in AVMs of the brain or face. Moreover, these trials demonstrated conflicting results: one found topical rapamycin effective in treatment of port-wine stains and Sturge-Weber syndrome and the other found topical rapamycin ineffective [18, 19]. Patients in our study were treated with a maximum dose of 40 mg rapamycin to achieve an optimum level of 3–20 ng/mL. However, further research is required to determine the efficacy, optimal dosage, and optimal treatment duration of rapamycin. One earlier study suggested rapamycin promoted coagulopathy in patients treated with low-flow AVMs based on correlation with significant decrease in D-dimer levels [25]. However, in a case series of both pediatric and adult patients, it was noted that children developed oral ulcers and oral mucositis following rapamycin treatment for extracranial AVMs [13]. Other authors also reported relatively infrequent and minor complications, such as transient hyperlipidemia and minor opportunistic infection [16]. Randomized controlled trials investigating both the safety profile and efficacy of rapamycin in AVM management would be helpful in this regard.

Other proposed medical treatments for AVMs focus on the disruption of the vascular endothelial growth factor and KRAS-mitogen activated protein kinase-extracellular signal regulated kinase pathway, which have been

Fig. 1. **a** A 23-year-old woman presented with difficulty opening her eye, pain, and swelling secondary to a left orbito-facial AVM. Curative surgery in this case would have involved extensive soft tissue dissection, and the patient wished to avoid undesirable cosmetic defects from open surgery. **b** The malformation prior to embolization was fed by branches of the facial and superficial temporal arteries as seen on anteroposterior projection of left external carotid injection (**b1**). Lateral projected view of internal carotid injection shows blood supply from the ophthalmic artery (**b2**). At 6-month follow-up after embolization and therapy with rapamycin, minimal residual contrast is visualized within the AVM on AP (**b3**) and lateral (**b4**) angiography of the external and internal carotid, respectively. **c** A 28-year-old woman with a right facial-orbital AVM presented with refractory epistaxis and left-sided retro-orbital pressure. She had previously undergone multiple opera-

tions, including enucleation of the right eye. The AVM was supplied by feeders arising from the internal maxillary, lingual, and superficial temporal arteries, as shown in the lateral external carotid injection (**c1**), and by the ophthalmic artery as shown in the lateral internal carotid injection (**c2**). In staged sessions, feeding pedicles including branches of the ophthalmic and sphenopalatine arteries were embolized and coiling of the ophthalmic artery aneurysm were performed. The patient subsequently initiated therapy with rapamycin. At 1-year follow-up, there was no significant increase in residual filling at the mandible from the facial and lingual arteries and the inferolateral trunk compared to what was seen following embolization (lateral projection of internal carotid injection (**c3**); lateral projection of external carotid injection (**c4**)). Epistaxis was noted to have ceased completely. AVM, arteriovenous malformation.

implicated in AVM formation [1, 20]. MEK inhibitors have been effective in treating AVM based on case reports, but may not be as effective as mTOR inhibitors because they accelerate angiogenesis through parallel stimulation of the mTOR pathway [6].

Other steps in the phosphatidylinositol-3-kinase (PIK-3)/protein kinase B/mTOR pathway, which promotes vascular maturation and stability, may offer other opportunities for targeted therapy [14]. The PIK-3/protein kinase B/mTOR pathway is mediated by the tyrosine kinase receptor TIE2

and its ligands, angiopoietin-1, and angiopoietin-2 [9]. *TIE2* mutations have been demonstrated in over half of all venous malformations [21]. A number of clinical trials evaluating the use of dactolisib, a dual PIK-3/mTOR inhibitor, are ongoing in treatment of various cancers [22].

Case Presentation

Case #1

A 23-years-old woman developed a left orbital-facial AVM which caused pain, difficulty with eye opening, and cosmetic worsening secondary to swelling and difficulty opening the eye (Fig. 1a). The malformation was fed by the left facial artery, left superior temporal artery, and left ophthalmic artery distal to the central retinal artery and included a prenidial fusiform aneurysm of the left ophthalmic artery distal to the origin of the central retinal artery. Venous drainage was via the superior ophthalmic veins, cavernous sinus, pterygopalatine fossa, and facial vein. The patient had seen ENT and plastic surgery teams but declined surgery out of concern for cosmetic disfigurement, opting for palliative embolization instead.

The distal ophthalmic artery aneurysm was coiled, and pedicles arising from the left facial artery, internal maxillary artery, and superficial temporal artery were embolized (Fig. 1b). Following embolization, there was a noted decrease in preoperative swelling over the patient's forehead and left eyelid. Postoperatively, the patient was placed on rapamycin 2 mg daily by mouth, adjusted for serum trough 5–15 ng/mL. At the 6-month angiogram, there remained minimum flow into the AVM, and swelling over the brow and eyelid had subsided completely.

Case #2

A 28-years-old woman with a longstanding facial-orbital AVM having previously undergone partial resection and right eye enucleation complicated by poor wound healing, presented to the emergency room with refractory epistaxis and retro-orbital pressure on the left. She had also previously undergone over 10 palliative embolization procedures at another hospital. Our institution's ENT team initially performed endonasal cauterization of bleeding sphenopalatine and ethmoidal arteries. The patient continued to have more than 3 episodes of epistaxis every month. Next, in 2 staged sessions, feeding pedicles including branches of the ophthalmic and sphenopalatine arteries were embolized and coiling of an ophthalmic artery aneurysm were performed (Fig. 1c). The patient continued to have epistaxis episodes every or every other month. The patient was then placed on rapamycin following intervention using our standard protocol.

Six months later, she underwent another combined plastic/ENT surgery for excision of other branches affecting the forehead and cheek, as well as laser cauterization of septal telangiectasias. She was noted to have minimal bleeding at the time of that operation. The patient was seen again at 1-year follow-up and was found to have an overall marked decrease in the size of the AVM, with small residual filling at the mandible from the facial and lingual arteries and the inferolateral trunk. Epistaxis is noted to have ceased completely, and she currently has no other AVM-related symptoms. Retro-orbital pressure had resolved and along with daily headaches.

Conclusion

Early results of treatment of inoperable AVMs of the head and face with medications that target molecular pathways in AVM development have been encouraging. We present 2 cases where adjuvant therapy with rapamycin prevented repeat intervention and review the literature surrounding rapamycin treatment in AVMs. Further studies regarding the efficacy of mTOR inhibitors for cranial and facial lesions may be worthwhile.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was received from the patients for publication of this case report and any images.

Conflict of Interest Statement

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Author Contributions

Each author contributed equally to the manuscript.

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