Effects of sirolimus in the treatment of unresectable infantile hemangioma and vascular malformations in children: A single-center experience

Yu Jeong Cho, MD, Hyunhee Kwon, MD, Yong Jae Kwon, MD, Seong Chul Kim, MD, PhD, Dae Yeon Kim, MD, PhD, *and* Jung-Man Namgoong, MD, PhD, *Seoul, Korea*

ABSTRACT

Objective: Recently, sirolimus has emerged as a safe and effective treatment modality for unresectable vascular lesions. In the present study, we investigated the effectiveness and safety of sirolimus from our early experience with patients with unresectable vascular anomalies.

Methods: The medical records and radiologic images of all patients with unresectable vascular anomalies treated with sirolimus at our center from January 2018 to November 2019 were retrospectively reviewed. All patients were administered oral doses of sirolimus 0.8 mg/m^2 every 12 hours as the initial dose, followed by maintenance of a target serum concentration (5-10 ng/mL) with therapeutic drug monitoring.

Results: Six patients with unresectable vascular anomalies were treated with sirolimus for ≥10 months. Their median age at the initiation of sirolimus treatment was 17 months (range, 8-67 months). The median duration of treatment was 13 months (range, 10-16 months). One patient had a good response, four had an intermediate response, and one had no response to sirolimus therapy. None of the patients had discontinued sirolimus therapy because of adverse effects.

Conclusions: Sirolimus can be used effectively and safely for patients with unresectable vascular anomalies. However, further prospective studies are warranted to evaluate the long-term effects of sirolimus and clarify the indications for early intervention. (J Vasc Surg Venous Lymphat Disord 2021;9:1488-94.)

Keywords: mTOR inhibitors; Pediatrics; Sirolimus; Vascular anomaly

Vascular anomalies are a heterogeneous group of disorders caused by anomalies in the development and anatomy of blood and/or lymphatic vessels. The International Society for the Study of Vascular Anomalies adopted a state-of-the-art classification system for vascular anomalies in 2014, with vascular tumors characterized by a proliferative component and vascular malformations by structural anomalies and innate errors of vascular morphogenesis. Vascular tumors are characterized by abnormal proliferation of endothelial cells and aberrant blood vessel architecture and are divided into three groups: benign, borderline, and malignant. The benign vascular tumor, infantile hemangioma (IH), is behaviorally and biologically distinct from other tumors such as congenital hemangioma, pyogenic granuloma, tufted angioma, and hemangioendothelioma. Vascular malformations are classified as capillary, venous, lymphatic, arteriovenous, or combined according to the vascular channels involved.[1]

As vascular anomalies develop, they can lead to body deformities and disfiguration, pain, recurrent bleeding, infection, heart failure, and, even, death. Venous malformations are associated with venous stasis and localized intravascular coagulopathy, increasing the likelihood of thromboembolic events, such as pulmonary emboli and localized or disseminated intravascular coagulation.[2] Microcystic lymphatic malformation (LM) combined with malformations of other vascular channels can cause severe morbidity and/or mortality owing to soft tissue disfigurement, bony abnormalities, and organ compromise.[1,3] Depending on the location of the malformation and the organs involved, the degree and symptoms of LM can vary widely. In most cases, cosmetic concerns for LMs will influence the treatment chosen. However, when LM occurs in the upper aerodigestive tract, the mass effect of the malformation can cause life-threatening airway obstructions, impair oral feeding, and lead to speech and communication difficulties.[4-6]

From the Department of Pediatric Surgery, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine.

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Correspondence: Dae Yeon Kim, MD, PhD, Department of Pediatric Surgery, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea (e-mail: spdykim@hotmail.com).

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The type of vascular anomaly determines the choice of treatment, which includes a wide variety of options, including propranolol, embolization, laser therapy, sclerotherapy, and surgical resection. However, these treatments can result in substantial morbidity, especially when addressing complicated vascular anomalies such as extensive vascular tumors or vascular malformations in vital organs that cannot be cured using conventional therapy or for which conventional therapies have failed.

To address the challenges of conventional treatment modalities for vascular malformations, less invasive approaches such as mammalian target of rapamycin (mTOR) inhibitors are being investigated.[2] The phosphoinositide 3-kinase/mTOR pathway is the basis of various cellular processes, including cellular metabolism, cell growth, and proliferation, and its pathway leads to the expression of vascular endothelial growth factor, the key regulator of angiogenesis and lymphangiogenesis.[2,7] Therefore, mTOR inhibitors such as sirolimus can block downstream protein synthesis and have antitumor and antiangiogenic effects.[8]

Sirolimus is the only mTOR inhibitor currently approved by the U.S. Food and Drug Administration. Sirolimus is generally used to prevent organ rejection after kidney transplantation in patients aged >13 years.[9] It is also used for patients with coronary artery disease or lymphangioleiomyomatosis-related lung disease. The diverse effects can have therapeutic applications for the treatment of other diseases, such as soft tissue and bone sarcomas and advanced lymphoma.[10] In 2010, sirolimus was introduced as an antiangiogenetic treatment in children with kaposiform hemangioendothelioma.[11] Only a few clinical studies have since been reported on the effects of sirolimus on vascular anomalies. These studies found that sirolimus could be considered a part of the safe management strategy in challenging patients in whom traditional therapies have failed.[3,7,11] In the present report, we have described our early experience using sirolimus to treat diffuse unresectable vascular anomalies and vascular anomalies considered unresectable because of invasion of vital organs.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective analysis of prospectively collected registry data
- **Key Findings:** Six patients with unresectable vascular anomalies that did not respond to conventional therapies were treated with sirolimus. A mass volume decrease occurred in five of six patients, ranging from 23% to 99.9%. No serious adverse effects associated with sirolimus were observed during treatment.
- **Take Home Message:** Sirolimus is a promising treatment that can be applied to unresectable vascular anomalies that are diffuse or that invade vital organs. These findings could be useful for the treatment of patients with refractory vascular anomalies by promoting a reduction in the size of the lesion and as a bridge to resection.

METHODS

The data from 18 patients with complicated vascular anomalies who had been treated with sirolimus from July 2018 to May 2019 at Asan Medical Center (Seoul, South Korea) were retrospectively reviewed. Because the present study was exploratory, statistical analyses were not performed. Data on patient demographics, type of vascular anomaly, location and range of the effects of the vascular anomaly, age at the first administration of sirolimus, self-reported (parent-reported) quality of life, the need for tracheostomy or gastrostomy, complications, and outcomes were collected from the medical records and documented until November 2019. The vascular anomalies were diagnosed from the clinical findings and confirmed using magnetic resonance imaging (MRI) and/or computed tomography, which had been obtained for all patients.

Sirolimus therapy was administered to (1) patients with vascular anomalies confirmed to be unresectable by the imaging or histologic studies because of proximity to a vital organ or interdigitating with contiguous structures; (2) patients whose had symptoms worsened or failed to improve on MRI and/or computed tomography studies after treatment according to the vascular anomaly type; and (3) patients with complications from vascular anomalies, such as frequent respiratory infections, coagulopathy, recurrent cellulitis (more than three episodes annually), visceral involvement, and/or cardiac dysfunction.

Sirolimus was administered orally using a liquid formulation or as a tablet, depending on the patient's age. The initial dose was 0.8 mg/m^2 per dose, administered every 12 hours, and, subsequently, adjusted to maintain a target 12-hour trough level of 5 to 10 ng/mL. We set a slightly lower target trough level than that of other studies (ie, 5-15 ng/mL) to decrease the risk of drug toxicity that could occur from a higher dosage.[2,7,11-15]

The primary outcome was the response to therapy, which was defined as a reduction in the bulk of the LM as determined by evaluating digital photographs and radiologic imaging studies. A baseline evaluation was conducted before initiating sirolimus therapy, and the response was evaluated at 6- and 12-month intervals. The lesion volume was calculated on MRI by measuring the greatest dimensions in the transverse axis and anteroposterior views, which was 90° to the transverse axis on the same slice and to the longitudinal axis. The formula used for calculating ellipsoid volume was as follows: ellipsoid volume = (transverse axis × anteroposterior view × longitudinal axis)/2.[16,17] This method of volume

Table I. Evaluation of disease response

Response	Description
Good	Improvement in radiologic imaging findings of >70% or remnant lesion in radiologic imaging but no gross lesion identified
Intermediate	Improvement in radiologic imaging findings ≤70% and >30% or self-reported improvement of gross lesion
Poor	Improvement in radiologic imaging findings of <30%, stable disease status, or self-reported worsening of gross lesion

measurement correlates with that obtained by drawing the outlines manually.[18-20] The volume reduction rate was calculated between the pre- and post-treatment lesion volumes. The patient response was defined as good, intermediate, and poor according to the findings from the digital photographs and radiologic imaging studies (Table I).

The severity of the complications was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0.[21] The parents of all the patients provided written informed consent for participation in the present study. All the procedures were performed in accordance with the ethical standards of the ethics committee of the Asan Medical Center (institutional review board approval no. 2020-0190).

RESULTS

Eighteen patients were treated with sirolimus for vascular anomalies from July 2018 to December 2019. Of the 18 patients, 6 had been administered sirolimus for ~1 year, allowing for sufficient time for the evaluation of the effects of sirolimus (Table II). The median age at the initiation of sirolimus was 17 months (range, 8-67 months). All six patients had been unsuccessfully treated using different modalities such as propranolol, sclerotherapy, and excision. The vascular anomaly had been diagnosed before birth in five of the six children by fetal ultrasonography. The patients with refractory head and neck LM had not responded well to sclerotherapy and resection. Of these six patients, one had a mixed macrocystic-microcystic LM, two had a microcystic LM, two had a lymphovenous malformation, and one had IH. All the patients had required tracheostomy owing to airway compression, and three patients had required gastrostomy owing to difficulty in receiving oral nutrition. One patient had had brain and systemic hemangiomas. The median treatment duration was 13 months (range, 10-16 months), and all the patients had continued sirolimus therapy through the end of the study period. Five patients had temporarily discontinued sirolimus during the treatment period (median time without sirolimus, 2 months; range, 1.4-3.5 months). Viral infection of the upper respiratory tract was the cause for all five patients, with obvious symptoms of infection and accompanied by fever. The interval to restarting sirolimus after stopping ranged from 7 to 35 days.

The mass volume had decreased in five of the six patients, with a volume reduction ranging from 23% to 99.9%. The patient with brain and systemic hemangiomas had experienced complete remission, and four patients with cervicofacial LMs had had partial remission. For the sixth patient, no overall volume reduction was seen on MRI. More dramatic imaging responses were seen for the younger patients who had not undergone previous procedures. The significant response to sirolimus for patient 1 with IH is shown in Fig 1. This patient had experienced anal bleeding from the perianal lesion early during sirolimus treatment, and the brain lesions had completely resolved after 6 months of sirolimus treatment. Patient 2 experienced moderate improvements in facial asymmetry and a decrease in lesion size (Fig 2). All five patients with cervicofacial LMs were dependent on the tracheostomy at sirolimus initiation. One experienced improved atelectasis because the LM involving the chest had decreased in size, and the patient's concurrent dependence on mechanical ventilation had resolved after 1 year of sirolimus treatment (Fig 3). Minor adverse effects, such as grade 1 stomatitis and dermatitis,[22] were identified in two patients; however, the lesions had healed without any intervention. One patient had consumed a beverage containing grapefruit extract and was required to discontinue sirolimus for 20 days owing to elevated therapeutic drug levels. None of the patients had developed systemic or opportunistic bacterial infections during the study period.

DISCUSSION

Sirolimus, an inhibitor of the mTOR pathway, decreases protein synthesis for cell proliferation and angiogenesis, which can inhibit the growth of vascular tumors. In addition, Greenberger et al[23] demonstrated that sirolimus diminishes the self-renewal capacity of IH-derived stem cells, activates the differentiation toward a perivascular cell phenotype, and inhibits angiogenesis from IH-derived stem cells.[23] Several recent studies have reported the effectiveness of sirolimus for the treatment of vascular malformations and vascular tumors, including IH, without the development of severe adverse effects.[7,13,14] Recently reported genetic studies have shown that somatic mutations in *PIK3CA* and vascular endothelial growth factor overexpression are found in syndromic LMs.[24,25] These studies found that sirolimus was effective in treating vascular anomalies that were refractory to standard care approaches, such as resection, sclerotherapy, propranolol, and steroids. In Korea, sirolimus has not yet been established as a treatment option for

Table II. Clinical characteristics and sirolimus treatment response for six patients

Pt. No.	Age at initiation, months	Sex	Diagnosis	Localization	Airway or GI tract compression	Previous treatment	Sirolimus duration, months	Improved symptoms	Complication	Volume reduction, %	Treatment response
1	12	M	IH	Brain, shoulder, chest, both arms, both legs, anus	No	Propranolol, prednisone	16	Anal bleeding resolved	Stomatitis, diarrhea	99	Good
2	67	F	LVM	Cervicofacial	Tracheostomy, gastrostomy	Sclerotherapy (OK-432 1×, doxycycline 4×), excision (3×)	15	Oral feeding improved, gastrostomy removal	No	Left, 32; right, UC	Left, intermediate; right, poor
3	20	M	Mixed LM	Cervicofacial, chest wall	Tracheostomy, gastrostomy	Sclerotherapy (doxycycline 9×; bleomycin 1×), excision (1×)	13	Decreased infections, decreased oxygen demand, gastrostomy removal	Dermatitis	30	Intermediate
4	54	F	Microcystic LM	Cervicofacial	Tracheostomy	Sclerotherapy (doxycycline 13×), excision (2×)	13	Decreased infection	No	UC	Poor
5	14	F	Microcystic LM	Cervicofacial	Tracheostomy	Excision (1×)	11	Decreased infection	No	39	Intermediate
6	8	M	LVM	Cervicofacial	Tracheostomy, gastrostomy	Sclerotherapy (doxycycline 3×), excision (1×)	10	Oral feeding improved, gastrostomy removal	No	Left, 79; right, 23	Left, good; right, poor

F, Female; *GI,* gastrointestinal; *IH,* infantile hemangioma; *LM,* lymphatic malformation; *LVM,* lymphovenous malformation; *M,* male; *Pt. No,* patient number; *UC,* unchanged.

vascular anomalies. We used this emerging treatment for the first time in Korea and applied it to selected patients to evaluate its effectiveness.

We found that the use of sirolimus was low risk and somewhat effective for patients who could not benefit from existing treatment modalities. The therapeutic

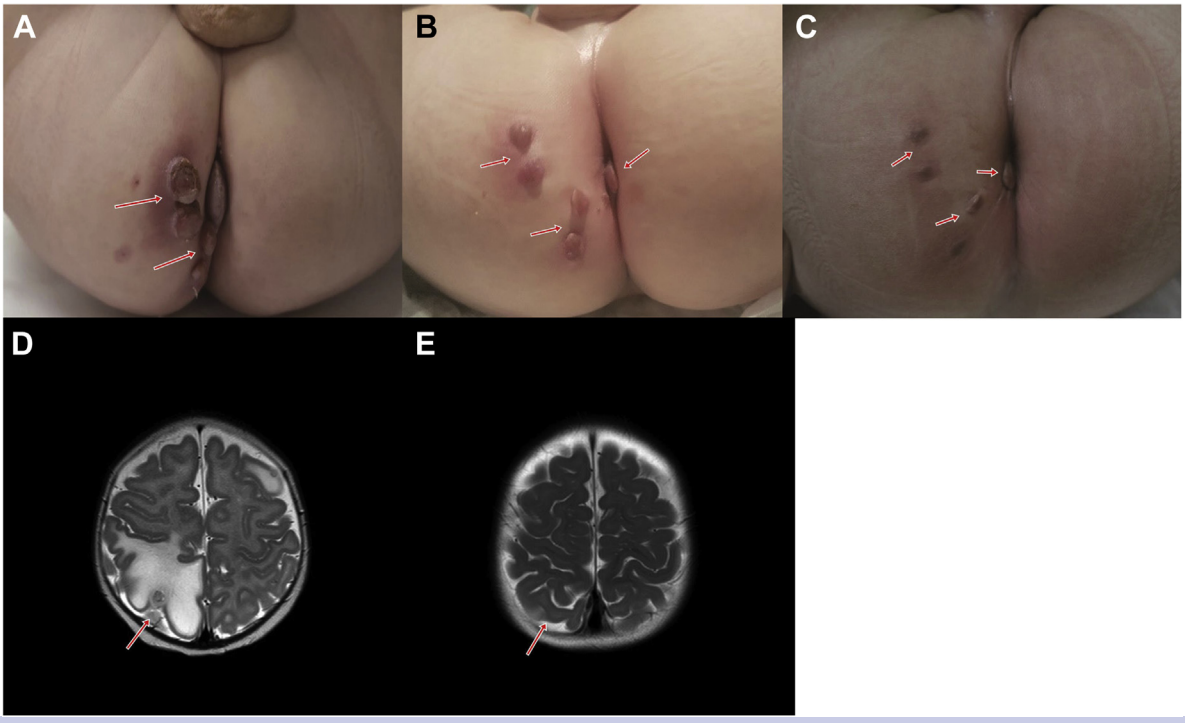

Fig 1. Patient 1 with infantile hemangioma (IH) affecting the whole body at the beginning of therapy **(A)**, after 3 months of sirolimus treatment **(B)**, and after 1 year of sirolimus therapy **(C)**. Axial T2-weighted magnetic resonance imaging (MRI) of patient 1 showing intracranial hemangioma before the initiation of sirolimus **(D)** and after 6 months of sirolimus therapy **(E)**.

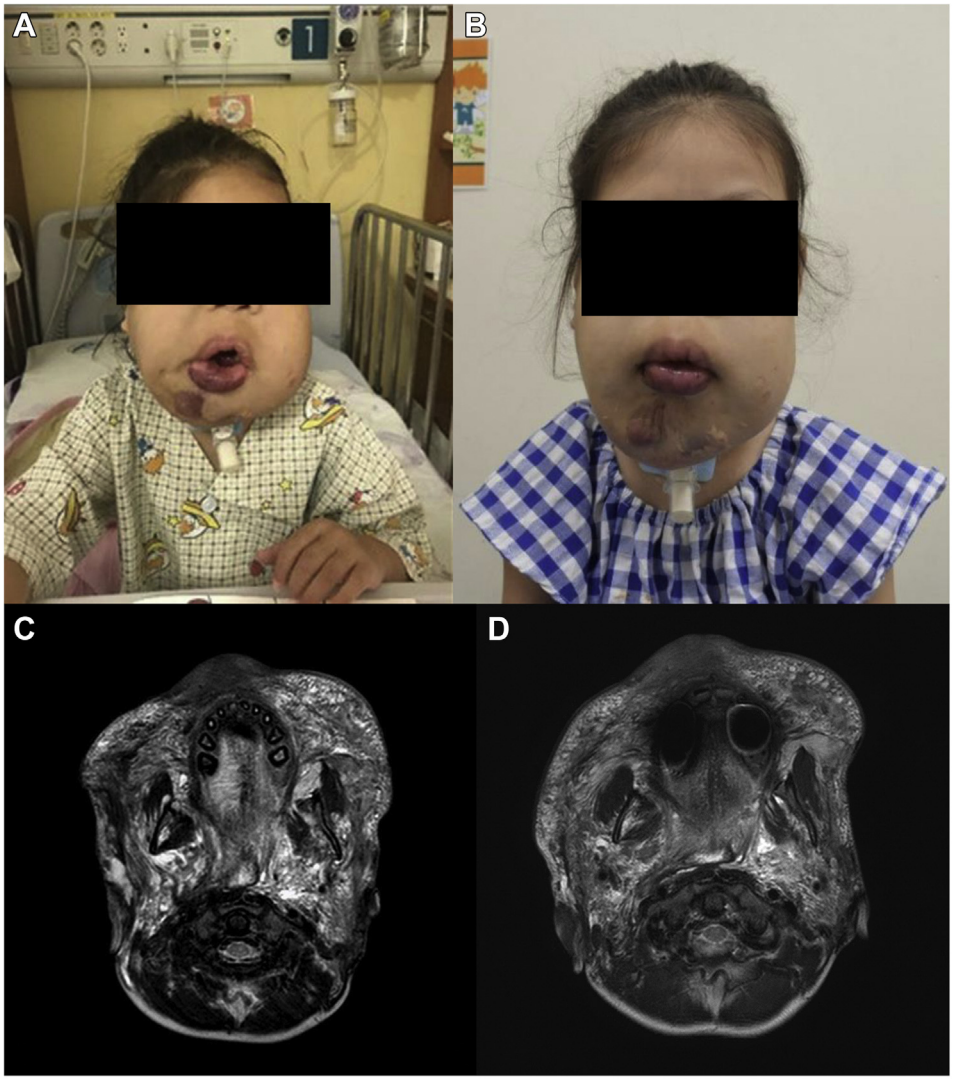

Fig 2. Clinical photographs of patient 2 showing a cervicofacial lymphovascular malformation before the initiation of sirolimus **(A)** and the interval decrease in the lesion size, with a decreased mucosal lesion after administration of sirolimus **(B)**. Axial T2-weighted magnetic resonance imaging (MRI) of patient 2 at the beginning of therapy **(C)** and at 10 months of sirolimus administration **(D)**.

effect (ie, the volume change in the target lesion) in our study was 20% to 99% and differed among the patients. Most patients in the present study had undergone multiple sclerotherapy sessions and one or more resections. Previous studies have shown that the older the patients and the more treatments they have undergone previously, the less the therapeutic effect of sirolimus.[12,14,26] Adams et al[14] suggested that the physiology of the lymphatic system might change during development, with the result that medical management becomes less effective over time. In addition, sclerosing agents, such as OK-432, doxycycline, and bleomycin used in our patients, have different mechanisms of action but eventually result in dense adhesions and fibrosis that transform cystic lesions into scar tissue, which could affect their response to sirolimus.[16,27]

The mucosal area and lesions close to vital organs were more responsive to sirolimus therapy because of the reduced likelihood of previous aggressive treatment in these areas. All the patients who had undergone gastrostomy because of the challenges in receiving oral nutrition due to the LM in the oropharynx were able to receive oral nutrition after removal of the gastrostomy tube. Of these patients, one patient (patient 2), who had experienced only a minor change in the lesion volume on radiologic evaluations, nevertheless demonstrated improved quality of life owing to the increased dietary volume and removal of the gastrostomy tube.

For cervicofacial lesions, surgery will usually be preferred.[4,28,29] In the present study, as reported in other studies, surgery was considered initially, if resection was

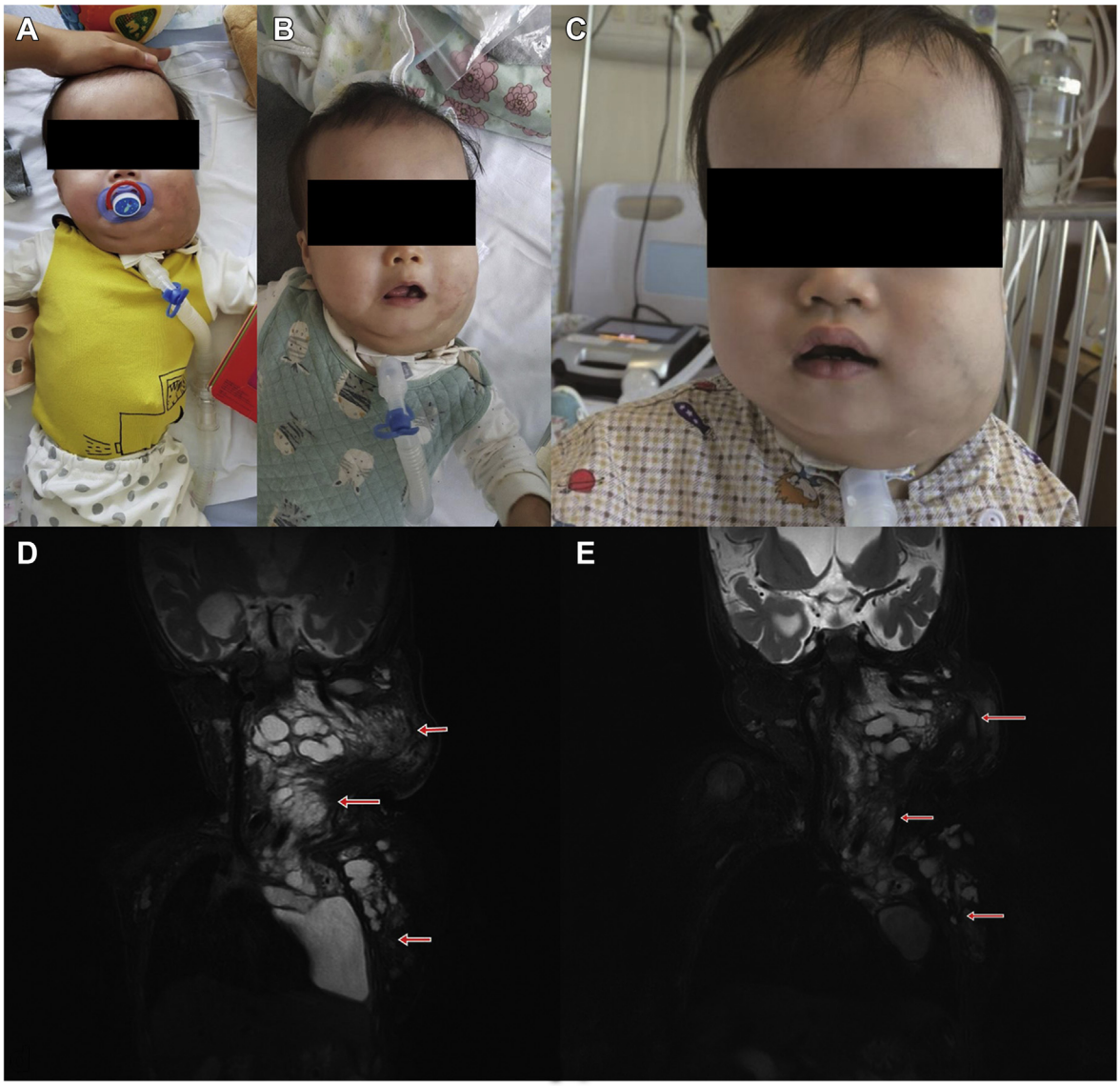

Fig 3. Serial clinical photographs of patient 1 showing a cervicofacial lymphatic malformation (LM) at the initiation of sirolimus **(A)**, at 2 months of administration **(B)**, and 6 months later **(C)**. Coronal T2-weighted magnetic resonance imaging (MRI) of patient 1 at the beginning of therapy **(D)** and at 1 year of sirolimus therapy **(E)**.

possible. In patient 4, debulking was partially effective. However, access was limited to the mediastinal lesion, which caused respiratory distress, and mechanical ventilation was continued after surgery. Sirolimus was administered because further improvement in symptoms from conventional treatment was not expected. Treatment with sirolimus, however, was effective in reducing the extent of the mediastinal lesion, and atelectasis had improved to the point that the patient could be weaned from mechanical ventilation (Fig 3). The findings from this patient have provided additional evidence for the potential use of sirolimus on large vascular malformations, not only to promote reduction of the lesion mass and improve symptoms, but also to act as a bridge to resection.

The known adverse effects of sirolimus include mucositis, rash, anorexia, gastrointestinal effects (eg, diarrhea and nausea), hematologic effects (eg, thrombocytopenia, leukopenia, anemia), and metabolic effects (eg, hyperlipidemia, hyperglycemia, hypercholesterolemia).[30,31] No serious adverse effects associated with sirolimus were observed during treatment. Some of the patients had required a period of temporary suspension of sirolimus owing to the development of upper respiratory infections. However, recurrent infections are common in patients with LMs. Hence, it would be difficult to attribute these infections to sirolimus therapy. We also found that the infections tended to be milder after sirolimus treatment had been initiated. Close laboratory and clinical monitoring showed that treatment with sirolimus

was well tolerated by the patients, and the adverse effects could be controlled using conservative treatment or by decreasing the sirolimus dosage.

CONCLUSIONS

Sirolimus is a promising treatment modality for unresectable vascular anomalies refractory to conventional therapy with low risk. Sirolimus is an innovative treatment option and should be considered as a potential alternative for the treatment of vascular anomalies. Further studies are required to evaluate its effects on long-term treatment outcomes, including the appropriate duration of sirolimus treatment, and to clarify the indications for early intervention.

AUTHOR CONTRIBUTIONS

Conception and design: YC, DK
Analysis and interpretation: YC, DK
Data collection: YC, HK, YK, SK, DK, JN
Writing the article: YC
Critical revision of the article: YC, HK, YK, SK, DK, JN
Final approval of the article: YC, HK, YK, SK, DK, JN
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Overall responsibility: DK

REFERENCES

1. Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. Pediatrics 2015;136:e203-14.
2. de Vasconcellos JF, Laranjeira AB, Zanchin NI, Otubo R, Vaz TH, Cardoso AA, et al. Increased CCL2 and IL-8 in the bone marrow microenvironment in acute lymphoblastic leukemia. Pediatr Blood Cancer 2011;56:568-77.
3. Yesil S, Tanyildiz HG, Bozkurt C, Cakmakci E, Sahin G. Single-center experience with sirolimus therapy for vascular malformations. Pediatr Hematol Oncol 2016;33:219-25.
4. Bajaj Y, Hewitt R, Ifeacho S, Hartley BE. Surgical excision as primary treatment modality for extensive cervicofacial lymphatic malformations in children. Int J Pediatr Otorhinolaryngol 2011;75:673-7.
5. Berg EE, Sobol SE, Jacobs I. Laryngeal obstruction by cervical and endolaryngeal lymphatic malformations in children: proposed staging system and review of treatment. Ann Otol Rhinol Laryngol 2013;122:575-81.
6. Balakrishnan K, Edwards TC, Perkins JA. Functional and symptom impacts of pediatric head and neck lymphatic malformations: developing a patient-derived instrument. Otolaryngol Head Neck Surg 2012;147:925-31.
7. Triana P, Dore M, Cerezo VN, Cervantes M, Sanchez AV, Ferrero MM, et al. Sirolimus in the treatment of vascular anomalies. Eur J Pediatr Surg 2017;27:86-90.
8. Hartford CM, Ratain MJ. Rapamycin: something old, something new, sometimes borrowed and now renewed. Clin Pharmacol Ther 2007;82:381-8.
9. Falger JC, Mueller T, Arbeiter K, Boehm M, Regele H, Balzar E, et al. Conversion from calcineurin inhibitor to sirolimus in pediatric chronic allograft nephropathy. Pediatr Transplant 2006;10:565-9.
10. Yang G, Yang L, Yang X, Shi X, Wang J, Liu Y, et al. Efficacy and safety of a mammalian target of rapamycin inhibitor in pediatric patients with tuberous sclerosis complex: a systematic review and meta-analysis. Exp Ther Med 2015;9:626-30.
11. Kushner BH, LaQuaglia MP, Wollner N, Meyers PA, Lindsley KL, Ghavimi F, et al. Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol 1996;14:1526-31.
12. Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC III. Sirolimus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. Laryngoscope 2018;128:269-76.
13. Lackner H, Karastaneva A, Schwinger W, Benesch M, Sovinz P, Seidel M, et al. Sirolimus for the treatment of children with various complicated vascular anomalies. Eur J Pediatr 2015;174:1579-84.
14. Adams DM, Trenor CC III, Hammill AM, Vinks AA, Patel MN, Chaudry G, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics 2016;137:e20153257.
15. Goldenberg DC, Carvas M, Adams D, Giannotti M, Gemperli R. Successful treatment of a complex vascular malformation with sirolimus and surgical resection. J Pediatr Hematol Oncol 2017;39:e191-5.
16. Tu JH, Do HM, Patel V, Yeom KW, Teng JMC. Sclerotherapy for lymphatic malformations of the head and neck in the pediatric population. J Neurointerv Surg 2017;9:1023-6.
17. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304-5.
18. James K, Eisenhauer E, Christian M, Terenziani M, Vena D, Muldal A, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. J Natl Cancer Inst 1999;91:523-8.
19. Mayr NA, Taoka T, Yuh WT, Denning LM, Zhen WK, Paulino AC, et al. Method and timing of tumor volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2002;52:14-22.
20. Wapnir IL, Barnard N, Wartenberg D, Greco RS. The inverse relationship between microvessel counts and tumor volume in breast cancer. Breast J 2001;7:184-8.
21. Yamamichi T, Oue T, Yonekura T, Owari M, Nakahata K, Umeda S, et al. Clinical application of indocyanine green (ICG) fluorescent imaging of hepatoblastoma. J Pediatr Surg 2015;50:833-6.
22. Cho YB, Lee WY, Park KJ, Kim M, Yoo HW, Yu CS. Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study. Cell Transplant 2013;22:279-85.
23. Greenberger S, Yuan S, Walsh LA, Boscolo E, Kang KT, Matthews B, et al. Rapamycin suppresses self-renewal and vasculogenic potential of stem cells isolated from infantile hemangioma. J Invest Dermatol 2011;131:2467-76.
24. Luks VL, Kamitaki N, Vivero MP, Uller W, Rab R, Bovee JV, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr 2015;166:1048-54.e1-5.
25. Laforgia N, Schettini F, De Mattia D, Martinelli D, Ladisa G, Favia V. Lymphatic malformation in newborns as the first sign of diffuse lymphangiomatosis: successful treatment with sirolimus. Neonatology 2016;109:52-5.
26. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: part I. J Am Acad Dermatol 2007;56:353-70. quiz 71-4.
27. Chaudry G, Guevara CJ, Rialon KL, Kerr C, Mulliken JB, Greene AK, et al. Safety and efficacy of bleomycin sclerotherapy for microcystic lymphatic malformation. Cardiovasc Intervent Radiol 2014;37:1476-81.
28. Alqahtani A, Nguyen LT, Flageole H, Shaw K, Laberge JM. 25 Years' experience with lymphangiomas in children. J Pediatr Surg 1999;34:1164-8.
29. Riechelmann H, Muehlfay G, Keck T, Mattfeldt T, Rettinger G. Total, subtotal, and partial surgical removal of cervicofacial lymphangiomas. Arch Otolaryngol Head Neck Surg 1999;125:643-8.
30. Napoli KL, Taylor PJ. From beach to bedside: history of the development of sirolimus. Ther Drug Monit 2001;23:559-86.
31. Yee KW, Zeng Z, Konopleva M, Verstovsek S, Ravandi F, Ferrajoli A, et al. Phase I/II study of the mammalian target of rapamycin inhibitor everolimus (RAD001) in patients with relapsed or refractory hematologic malignancies. Clin Cancer Res 2006;12:5165-73.

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