Published in final edited form as:

J Am Acad Dermatol. 2014 June ; 70(6): 1050–1057. doi:10.1016/j.jaad.2014.02.005.

An open-label study to evaluate sildenafil for the treatment of lymphatic malformations

Christina Danial, BA¹, Andrea L Tichy, PhD¹, Umar Tariq, MBBS², Glenda L Swetman, MD¹,
Phuong Khuu, MD¹, Thomas Leung, MD, PhD¹, Latanya Benjamin, MD¹, Joyce Teng, MD,
PhD¹, Shreyas S Vasanawala, MD, PhD², and Alfred T Lane, MD, MA¹

¹Department of Dermatology, Lucile Packard Children's Hospital at the Stanford University
School of Medicine, Palo Alto, CA

²Department of Radiology, Stanford University School of Medicine, Stanford, CA

Abstract

Background—Lymphatic malformations (LM) can be challenging to treat. Mainstay interventions including surgery and sclerotherapy are invasive and can result in local recurrence and complications.

Objective—To assess the effect of 20 weeks of oral sildenafil on reducing LM volume and symptoms in children.

Methods—Seven children (4 boys, 3 girls; ages 13–85 months) with LMs were given oral sildenafil for 20 weeks in this open-label study. The volume of the LM was calculated blindly using magnetic resonance imaging performed before and after 20 weeks of sildenafil. LMs were assessed clinically on weeks 4, 12, 20, and 32. Both the physician and parents evaluated the LM in comparison to baseline.

Results—Four subjects had a LM volume decrease (1.0–31.7%). In 2 subjects, despite a LM volume increase (1.1–3.7%), clinical improvement was noted while on sildenafil. One subject had a 29.6% increase in LM volume and no therapeutic response. LMs of all 6 subjects who experienced a therapeutic response on sildenafil softened and became easily compressible. Adverse events were minimal.

© 2014 American Academy of Dermatology, Inc. Published by Mosby, Inc. All rights reserved.

Address correspondence to: Alfred T Lane, MD, Department of Dermatology, Stanford University School of Medicine, 700 Welch Rd, Suite 301, Palo Alto, CA, 94304, alfred.lane@stanford.edu, Phone: (650) 721-7170, Fax: (650) 724-2491.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: All authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: All authors have no conflicts of interest to declare.

Clinical Trial Registration: A study to evaluate sildenafil for the treatment of lymphatic malformations (NCT01290484); Registration date: February 3, 2011.

Prior Presentation: This study was presented at the 2013 International Investigative Dermatology Conference in Edinburgh, Scotland and at the 2013 Translational Science Conference in Washington, DC.

Limitations—A randomized-controlled trial will be necessary to verify the effects of sildenafil on LMs.

Conclusions—Sildenafil can reduce LM volume and symptoms in some children.

Keywords

Congenital; Lymphatic malformation; Macrocystic; Magnetic resonance imaging; Microcystic; Phosphodiesterase 5 inhibitors; Sclerotherapy

Introduction

Cystic lymphatic malformations (LM) are localized areas of abnormal development of the lymphatic system.¹ The cysts are classified as macrocystic, microcystic, or mixed based on their size.² There is great variability in the clinical course and associated complications of LMs, depending on location. Patients can present with visible deformity, pain, symptoms related to compression on adjacent structures, or sudden enlargement of the LM due to hemorrhage or infection.^{2, 3}

The treatment of LMs is rarely curative.^{2, 4} Surgery is not always possible since LMs can be intertwined within muscles or organs, and incomplete resection of LMs can result in recurrence.^{3, 5} Sclerosants such as ethanol, doxycycline, bleomycin, and OK-432 are less effective for treating microcystic and mixed lesions. Although macrocystic lesions may respond well initially, patients often need repeated sclerotherapy treatments over the course of their lifetime.^{2, 6} The efficacy of oral medications for the treatment of LMs, including sirolimus and propranolol, requires further investigation.^{7–10}

Recently, we reported marked regression of LMs in 3 children after treatment with oral sildenafil, a selective inhibitor of phosphodiesterase-5.¹¹ We extended the study to objectively assess the effect of sildenafil on reducing LM volume and symptoms in 7 additional children by using magnetic resonance imaging (MRI) volume segmentation analysis to quantify LM volume changes in response to 20 weeks of sildenafil.

Methods

Participants

An open-label study was conducted at a single institution between June 2011 and April 2013. Approval was obtained from the institutional review board of the Stanford University School of Medicine, and the trial was conducted at the Lucile Packard Children's Hospital. Written informed consent and assent were obtained from parents and children.

Male and female subjects between the ages of 6 months and 10 years were eligible to participate if they weighed at least 8 kg and had been diagnosed with a LM of at least 3 cm based on clinical and radiologic criteria. Macrocystic, microcystic, or mixed LMs involving any location of the body were included. LMs associated with an incomplete response to previous treatments, a risk of functional or aesthetic impairment, or local complications were included. All subjects were required to have normal blood, liver, and kidney function

tests, and a baseline ophthalmologic examination, prior to enrollment. Audiology examinations were performed at screening or at early subsequent study visits. The protocol was written to exclude subjects if they had a medical condition that may have interfered with their ability to complete the study, were allergic to sildenafil, required concomitant use of a medication contraindicated with sildenafil, or presented with a medical condition in which the use of sildenafil is contraindicated. Subjects with syndromes associated with a higher frequency of LMs and more complicated subjects with multiple medical comorbidities were excluded. All subjects had a baseline MRI examination at least 6 months prior to the commencement of sildenafil.

Study Design

At baseline (week 0), subjects began sildenafil (Revatio®; Pfizer, New York, New York) at a dose administered 3 times daily or about every 8 hours (Fig 1). Dosing was based on the European Medicines Agency (EMA) guidelines as follows: if the subject weighed more than 20 kg, then 20 mg was given 3 times daily (60 mg/day); if the subject weighed between 8 kg and 20 kg, then 10 mg was given 3 times daily (30 mg/day). Baseline physical examinations were performed, and vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and basal body temperature were obtained prior to initiating sildenafil. The initial dose of sildenafil was dispensed in an outpatient clinic, and vital signs were monitored every 30 minutes during a 2-hour observation period. For children unable to swallow the medication, sildenafil was crushed and mixed into sweet syrup or other liquid. The dosage was adjusted for weight at each study visit. Subjects were evaluated in clinic on weeks 4, 12, and 20 and were contacted by phone on weeks 2, 8, and 16 (Fig 1). At week 20 (end of treatment), subjects were instructed to stop sildenafil. Subjects were examined 12 weeks after the last dose (week 32).

Outcome Measures

The primary outcome was the effect of sildenafil on LM volume. Response to sildenafil was characterized by any decrease in LM volume. LM volumes were assessed blindly by MRI volume segmentation analysis at baseline and after 20 weeks of sildenafil.¹² MRI examinations were performed under general anesthesia. MRI examination protocols included T1-, T2-, and contrast-material (gadolinium-based) enhanced T1-weighted images in the axial and coronal planes. All images were sent to an independent workstation with real-time multiplanar reformation capability (Osirix; Geneva, Switzerland).¹² A senior pediatric radiologist blindly calculated LM volume on baseline and week 20 MRI examinations using MRI volume segmentation analysis, which consisted of outlining the circumference of the lesion on each consecutive image that spanned the entire lesion. The total volume of the LM was calculated on the aggregate of the individual segmentations. The percentage of macrocysts in the LM was determined using baseline MRI examinations. Estimates of microcystic and mixed components were not performed due to the lower accuracy of these estimates with MRI software.

Secondary outcomes included both physician and parent assessments of LM improvement compared to baseline. At each study visit (weeks 4, 12, 20, 32), the physician and parents were asked to evaluate the change in texture, distortion of normal anatomy, and overall

change in comparison with baseline. Photographs of the LM at baseline were provided for comparison. A five-point Likert scale (no improvement (0%), minimal improvement (1–25%), fair improvement (>25–50%), good improvement (>50–75%), excellent improvement (>75–100%)) was used for responses. Complications associated with LMs prior to the initiation of sildenafil were reviewed and recorded. Any improvement or progression of these complications was noted at each study visit. Medication diaries were reviewed, and all adverse events recorded.

Results

Seven subjects (N=7) were enrolled in the study and completed the trial. The baseline demographic and clinical characteristics of the participants are shown in Table I. There were 4 boys and 3 girls, ranging in age from 13 months to 7 years at enrollment. Six subjects had a LM located in the head/neck, and one subject had a LM located in the abdomen. LM complications prior to sildenafil initiation included infection (N=3), hemorrhage (N=1), and obstruction of anatomical structures (N=1). Previous LM interventions included surgery (N=2) and doxycycline sclerotherapy (N=2). The percentage of macrocysts in each LM is shown in Table II.

All subjects completed 20 weeks of sildenafil (mean=22 weeks). Subjects who were unable to complete an MRI at week 20 due to scheduling, illness, or other personal obligations continued to take sildenafil until an MRI was performed. All subjects had a baseline MRI examination within 6 months prior to enrollment (mean=3.1 months).

Using MRI volume segmentation analysis, 4 subjects had a LM volume decrease (1.0–31.7%) (Table II). In 2 children (subjects 1 and 6), clinical improvement was noted while on sildenafil despite a LM volume increase (1.1–3.7%). Prior to initiating sildenafil, subject 1 had failed auditory tests due to infiltration of the LM in her right ear canal and experienced obstructive sleep apnea and airway occlusion while turning her neck due to the mass effect of the LM on the larynx. After 20 weeks of sildenafil, her right ear canal became completely visible, and there were no episodes of airway occlusion. Her apnea-hypopnea index improved from 8.8 (moderate apnea) with 25 episodes of obstructive sleep apnea with hypoxemia at baseline to 2.9 (mild apnea) with no episodes of apnea after 20 weeks of sildenafil. Subject 6 appeared to have shrinkage and softening of his LM despite the 1.1% increase in LM volume. This increase may have been related to inflammation from an upper-respiratory infection that he was experiencing at his end of treatment MRI. One child (subject 7) had a 29.4% LM volume increase and experienced no therapeutic response. Response to sildenafil was not associated with the percentage of macrocysts. Subjects 4 and 5 who had a 31.7% and 21.7% decrease in LM volumes had LMs with 1.6% and 76.0% of macrocysts, respectively (Table II).

Lymphatic malformations softened and became easily compressible in subjects 1–6. The parents and physicians reported improvement in tenseness/texture of the LM, and 5/6 subjects reported overall improvement compared to baseline. The parents of subject 4, who had a 31.7% decrease in LM volume, noted that she was more confident with her appearance at the end of the study (Fig 2). At week 20, the LM of subject 5 was soft and its borders

were difficult to identify. His parents rated a 50–75% improvement in tenseness/texture and a 75–100% overall improvement at week 20 compared to baseline. There was no clinically apparent increase in size from weeks 20 to 32 while subjects were off sildenafil.

There were no complications during treatment that warranted withdrawal from the study. Prior to initiating sildenafil, subject 2 had multiple hospitalizations for acute abdominal pain from LM infection after episodes of flu-like illness. While on sildenafil, there were no episodes of abdominal discomfort or LM infection, despite 2 flu-like episodes.

Adverse events reported while on sildenafil were minimal (Table III). All subjects tolerated the prescribed medication dose. During the study, subject 3 developed an upper respiratory tract infection and temporary hearing loss secondary to fluid accumulation in her left middle ear. Fluid accumulation resolved completely, and she experienced no further hearing loss while on sildenafil. Four parents (of subjects 1–4) requested to have the child continue sildenafil after study completion due to their impression of improvement in the LM and minimal side effects in comparison with prior interventions. Subjects 5 and 6 continued to show improvement at week 32 and decided to monitor for rebound enlargement. Subject 7 discontinued sildenafil after the 20-week period.

Discussion

These results are consistent with our previous report and further demonstrate that sildenafil is well tolerated and can be of benefit in the treatment of LMs.

Softening in the LM appeared to contribute to the symptomatic improvement in 6 subjects. The resolution of life-threatening episodes of sleep apnea, airway obstruction, and frequent infection was likely secondary to LM softening. The recent use of sildenafil for orbital LMs further demonstrates that sildenafil can decrease symptomatic LM swelling.¹³ It is unclear why the LM in subject 7 continued to expand while on sildenafil. There were no unique imaging features of the LM in this subject compared with other patients. Decreased LM volume was observed on sildenafil in both macrocystic- and microcystic- predominant lesions. Therefore, inherent biologic differences other than cyst size may exist in LMs that impact response to sildenafil.

The rate of progression of the LMs prior to the initiation of sildenafil is unknown. Several hypotheses about LM progression exist including growth by lymphangiogenesis, excessive fluid secretion, poor drainage, lymphatic aggregation, and cellulitis.^{4, 14} Sildenafil may slow the growth of the LM. If so, a longer course of sildenafil may permit volume changes to become more evident. A 20-week medication period was selected because our initial observations showed benefit from sildenafil within 8 to 12 weeks.¹¹ The optimal duration of treatment remains to be established.

The morphology and distribution of the LM may affect the response to sildenafil. It has been suggested that diffuse LMs have a greater likelihood of progression than focal lesions.⁴ Diffuse LMs may have a greater proinflammatory immune activity than smaller lesions and produce more urinary matrix metalloproteinases and basic fibroblast growth factor, indicating increased destruction and remodeling of the extracellular matrices.^{15, 16} Subjects

1 and 2 had diffuse lesions involving the head/neck and abdomen respectively (Table IV). Subjects with extensive LMs may require a longer treatment course or a higher dose of sildenafil to experience a larger decrease in LM volume. Subjects 4 and 5 had focal LMs and responded best to sildenafil based on LM volume change.

The mechanism of action remains unclear. Sildenafil selectively inhibits phosphodiesterase-5 preventing the breakdown of cyclic guanosine monophosphate. Inhibition of phosphodiesterase-5 decreases the contractility of vascular smooth muscle, producing vasodilation.¹⁷ A potential explanation for the therapeutic effect seen in these subjects is that the relaxation of the lymphatic vasculature may allow lymphatic spaces to open, decreasing LM volume. Although it is possible that previous surgery or sclerotherapy may have produced scarring that could decrease the ability of the lymphatic vasculature to relax with sildenafil, response to sildenafil was not related to a history of previous LM treatments (Table IV). Subject 4 had four sclerotherapy sessions prior to enrolling in the study and had the best response on sildenafil.

In order to limit the risks of anesthesia, MRI examinations performed within 6 months prior to the commencement of sildenafil were accepted to calculate the baseline LM volume. LMs may have changed size between the baseline MRI and enrollment in the trial, making MRI volume segmentation analysis less accurate than if all subjects had an MRI performed at baseline. Several subjects took sildenafil for more than 20 weeks due to MRI scheduling and personal accommodations. We did not identify that slight variations in the duration of sildenafil affected LM volume change. MRI volume segmentation was necessary to quantify changes in LM volume since physical examination or photography could not detect orthogonal or bidirectional changes.

A comparative, randomized placebo-controlled trial with a greater number of subjects is needed to confirm the benefit of sildenafil and to determine which LMs respond best. Optimal duration of treatment and dosage regimen needs to be examined further. Sildenafil may be a potential non-invasive therapeutic alternative for LMs. An effective oral medication for treatment of LMs would motivate additional research and could lead to further knowledge of the mechanisms underlying LMs.

Acknowledgments

The project described was supported by the National Center for Research Resources and the National Center for Advocacy Translational Sciences, National Institutes of Health, through UL1 TR000093 (formerly UL1 RR025744). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All phases of this study were supported by the following: SPARK, Spectrum—the Stanford Center for Clinical and Translational Research and Education; Lucile Packard Foundation for Children's Health; the Stanford NIH/NCCR Clinical Translational Science Award grant number TLI RR025742; and the Stanford University Medical Scholars Research Program.

We thank Pfizer for its support in providing Revatio®.

Abbreviations

EMA European Medicines Agency

FDA	Food and Drug Administration
LM	lymphatic malformation
MRI	magnetic resonance imaging
PAH	pulmonary arterial hypertension

References

1. Bloom DC, Perkins JA, Manning SC. Management of lymphatic malformations and macroglossia: results of a national treatment survey. *Int J Pediatr Otorhinolaryngol.* 2009; 73:1114–1118. [PubMed: 19515431]
2. Choi DJ, Alomari AI, Chaudry G, Orbach DB. Neurointerventional management of low-flow vascular malformations of the head and neck. *Neuroimaging Clin N Am.* 2009; 19:199–218. [PubMed: 19442906]
3. Cahill AM, Nijs E, Ballah D, Rabinowitz D, Thompson L, Rintoul N, et al. Percutaneous sclerotherapy in neonatal and infant head and neck lymphatic malformations: a single center experience. *J Pediatr Surg.* 2011; 46:2083–2095. [PubMed: 22075337]
4. Hassanein AH, Mulliken JB, Fishman SJ, Quatrano NA, Zurakowski D, Greene AK. Lymphatic malformation: risk of progression during childhood and adolescence. *J Craniofac Surg.* 2012; 23:149–152. [PubMed: 22337394]
5. Faul JL, Berry GJ, Colby TV, Ruoss SJ, Walter MB, Rosen GD, et al. Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. *Am J Respir Crit Care Med.* 2000; 161:1037–1046. [PubMed: 10712360]
6. Greene AK, Perlyn CA, Alomari AI. Management of lymphatic malformations. *Clin Plast Surg.* 2011; 38:75–82. [PubMed: 21095473]
7. Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, Elluru R, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer.* 2011; 57:1018–1024. [PubMed: 21445948]
8. Reinglas J, Ramphal R, Bromwich M. The successful management of diffuse lymphangiomatosis using sirolimus: a case report. *Laryngoscope.* 2011; 121:1851–1854. [PubMed: 22024836]
9. Ozeki M, Kanda K, Kawamoto N, Ohnishi H, Fujino A, Hirayama M, et al. Propranolol as an alternative treatment option for pediatric lymphatic malformation. *Tohoku J Exp Med.* 2013; 229:61–66. [PubMed: 23257321]
10. Maruani A, Brown S, Lorette G, Pondaven-Letourmy S, Herbreteau D, Eisenbaum A. Lack of effect of propranolol in the treatment of lymphangioma in two children. *Pediatr Dermatol.* 2013; 30:383–385. [PubMed: 23005572]
11. Swetman GL, Berk DR, Vasanawala SS, Feinstein JA, Lane AT, Bruckner AL. Sildenafil for severe lymphatic malformations. *N Engl J Med.* 2012; 366:384–386. [PubMed: 22276841]
12. Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging.* 2004; 17:205–216. [PubMed: 15534753]
13. Gandhi NG, Lin LK, O'Hara M. Sildenafil for pediatric orbital lymphangioma. *JAMA Ophthalmol.* 2013
14. Tammela T, Saaristo A, Lohela M, Morisada T, Tornberg J, Norrmen C, et al. Angiopoietin-1 promotes lymphatic sprouting and hyperplasia. *Blood.* 2005; 105:4642–4648. [PubMed: 15746084]
15. Marler JJ, Fishman SJ, Kilroy SM, Fang J, Upton J, Mulliken JB, et al. Increased expression of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. *Pediatrics.* 2005; 116:38–45. [PubMed: 15995028]
16. Fleming JN, Hostikka SL, Chen EY, Schwartz SM, Perkins JA. Plasmacytoid dendritic cells and interferon levels are increased in lymphatic malformations. *Otolaryngol Head Neck Surg.* 2008; 139:671–676. [PubMed: 18984262]

17. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med.* 1998; 338:1397–1404. [PubMed: 9580646]

Capsule Summary

- Current interventions for lymphatic malformations are invasive and have a risk of recurrence and complications.
- In this open-label study, sildenafil decreased lymphatic malformation volume and symptoms in some children and was well tolerated.
- Oral sildenafil is a potential non-invasive therapeutic alternative for lymphatic malformations.

Figure 1.
Clinical Trial Diagram. *MRI*, magnetic resonance imaging

Figure 2. Lymphatic malformation (LM). Photographs of subject 4 at baseline (2A, 2C) and after 20-weeks of sildenafil (2B, 2D). Coronal T2-weighted fat-suppressed magnetic resonance images show a microcystic-predominant LM in the left superficial pre-mandibular and pre-maxillary soft tissues at baseline (2E) that decreased by 31.7% in volume after 20 weeks of sildenafil (2F).

Table I

Baseline Demographics and Clinical Characteristics

	Subjects (N=7)
Male sex-no. (%)	4 (57.1)
Age	
Mean, months (range)	51.3 (13–85)
Weight at baseline	
Mean, kg (range)	17.0 (9.7–24.2)
LM location	
Head/Neck	6 (85.7)
Abdomen	1 (14.3)
Family history of LM-no. (%)	2 (28.6)
Previous LM treatment-no. (%)	
Surgery	2 (28.6)
Sclerotherapy	2 (28.6)
Previous LM complications -no. (%)	
Infections	3 (42.9)
Hemorrhage	1 (14.3)
Obstruction of anatomical structures	1 (14.3)
Lymphangioma circumscriptum* -no. (%)	3 (42.9)
Age at onset of LM	
Mean, months (range)	1.1 (0–6)

LM, lymphatic malformation

* Morphologic term used to denote a cutaneous microcystic LM, with or without a deeper macrocystic component

Table II

Percent Change in Lymphatic Malformation Volume

Subject	Volume of LM		Volume Difference (mL)	Volume Change (%)	Macrocystic component (%)
	Baseline (mL)	End of Treatment (mL)			
1	179.4	186.1	+6.7	+3.7	61.0
2	1453.7	1391.3	-62.4	-4.3	69.2
3	25.2	25.0	-0.2	-1.0	50.3
4	62.2	42.5	-19.7	-31.7	1.6
5	44.8	35.1	-9.7	-21.7	76.0
6	27.2	27.5	+0.3	+1.1	72.6
7	243.0	315.0	+72.0	+29.6	<10.0

LM, lymphatic malformation

Table III

Adverse events

Adverse Event	Subject, N
Nausea/Indigestion	4
Rhinorrhea	3
Cough	3
Mild insomnia	3
Fever	2
Emesis	2
Diarrhea	2
Flushing	1
Epistaxis	1
Prolonged erections	1
Temporary hearing illness	1
Photosensitivity	1
Bleeding into lymphangioma circumscriptum*	1

* Morphologic term used to denote a cutaneous microcystic LM, with or without a deeper macrocystic component

Table IV

Clinical Characteristics of 7 Subjects

Subject	1	2	3	4	5	6	7
Sex	Female	Male	Female	Female	Male	Male	Male
Age (months)	13	82	39	85	28	79	33
Weight (kg)	9.7	20.6	13.4	20.6	16.1	24.2	14.1
Family History of LM	None	None	None	None	Mother (uterus)	Grandmother (both sides of face, neck); aunt (right face)	None
LM Location	Right ear canal extending to involve the right supraclavicular area and larynx	Abdomen involving the small and large bowel, liver, bladder, and gallbladder	Superficial left pre-mandibular area and pre-maxillary soft tissues	Right masseter muscle extending to involve posterior parotid gland	Right submandibular area, superficial to right temporalis and masseter muscles	Right side of neck anterior to sternocleidomastoid muscle, submandibular gland	Left aspect of neck extending medially to involve submandibular, parapharyngeal, and masticator spaces
Age at Onset of LM (months)	Birth	Birth	Birth	Birth	Birth	6 months	2 months
Previous LM Treatment	Surgery (x1)	Doxycycline sclerotherapy (x2)	Surgery (x1)	Doxycycline Sclerotherapy (x4)	None	None	None
Previous LM Complications	Infection; Hearing deficit; Obstructive sleep apnea with hypoxemia; Airway Obstruction; Snoring	Infection; Acute abdominal pain; Ascites	Infection; Lymphangioma * circumscriptum	Lymphangioma * circumscriptum	Hemorrhage into LM	Lymphangioma * circumscriptum	None
Dose of sildenafil (mg/day)	30	60	30	60	30	60	30
Weeks of sildenafil	21	34	20	20	20	21	20
Adverse events on sildenafil	Nausea; Rhinorrhea; Mild insomnia; Cough; Fever; Emesis; Diarrhea	Nausea; Rhinorrhea; Mild insomnia; Cough; Emesis; Photosensitivity	Temporary hearing illness; Bleeding into lymphangioma * circumscriptum	Nausea; Flushing	Nausea/Indigestion; Mild insomnia; Fever; Prolonged erection	Epistaxis	Rhinorrhea; Cough; Diarrhea
MRI Volume Pre-treatment (mL)	179.4	1453.7	25.2	62.2	44.8	27.2	243.0
MRI Volume Post-treatment (mL)	186.1	1391.3	25.0	42.5	35.1	27.5	315.0
Change in volume (%)	+3.7	-4.3	-1.0	-31.7	-21.7	+1.1	+29.6
Macrocystic component (%)	61.0	69.2	50.3	1.6	76.0	72.6	<10.0

LM, lymphatic malformation; *MRI*, magnetic resonance imaging

* Morphologic term used to denote a cutaneous microcystic LM, with or without a deeper macrocystic component