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

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

Objective: We sought to assess the effect of 20 weeks of oral sildenafil on reducing lymphatic malformation volume and symptoms in children.

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

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

Limitations: A randomized controlled trial will be necessary to verify the effects of sildenafil on lymphatic malformations.

Conclusions: Sildenafil can reduce lymphatic malformation volume and symptoms in some children. (J Am Acad Dermatol 2014;70:1050-7.)

Key words: congenital; lymphatic malformation; macrocystic; magnetic resonance imaging; microcystic; phosphodiesterase-5 inhibitors; sclerotherapy.

Cystic lymphatic malformations 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 lymphatic malformations, depending on location. Patients can present with visible deformity, pain, symptoms related to

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compression on adjacent structures, or sudden enlargement of the lymphatic malformation caused by hemorrhage or infection.[2,3]

The treatment of lymphatic malformations is rarely curative.[2,4] Surgery is not always possible because lymphatic malformations can be intertwined within muscles or organs, and incomplete resection of lymphatic malformations 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 lymphatic malformations, including sirolimus and propranolol, requires further investigation.[7-10]

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 noninvasive therapeutic alternative for lymphatic malformations.

Recently, we reported marked regression of lymphatic malformations 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 lymphatic malformation volume and symptoms in 7 additional children by using magnetic resonance imaging (MRI) volume segmentation analysis to quantify lymphatic malformation 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, Stanford, CA, and the trial was conducted at the Lucile Packard Children's Hospital, Palo Alto, CA. Written informed consent and assent were obtained from parents and children. The trial was registered in http://www.clinicaltrials.gov on February 3, 2011 (NCT01290484).

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 given a diagnosis of a lymphatic malformation of at least 3 cm based on clinical and radiologic criteria. Macrocystic, microcystic, or mixed lymphatic malformations involving any location of the body were included. Lymphatic malformations 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, before 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 lymphatic malformations and more complicated subjects with multiple medical comorbidities were excluded. All subjects had a baseline MRI examination at least 6 months before the commencement of sildenafil.

Study design

At baseline (week 0), subjects began sildenafil (Revatio, Pfizer, New York, NY) at a dose administered 3 times daily or about every 8 hours (Fig 1). Dosing was based on the European Medicines Agency guidelines as follows: if the subject weighed more than 20 kg, then 20 mg was given 3 times daily (60 mg/d); if the subject weighed between 8 kg and 20 kg, then 10 mg was given 3 times daily (30 mg/d). Baseline physical examinations were performed, and vital signs including blood pressure, heart rate, respiratory rate, oxygen saturation, and basal body temperature were obtained before 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 telephone 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 lymphatic malformation volume. Response to

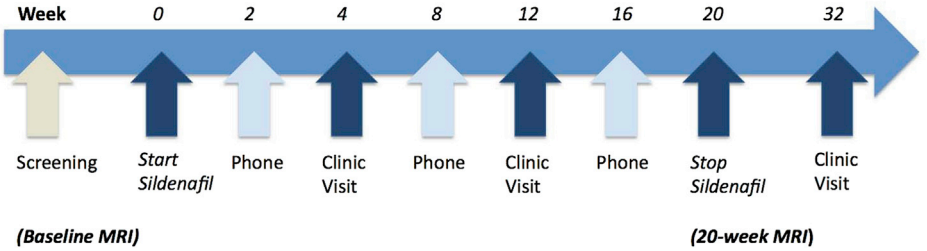

Fig 1. Clinical trial diagram. *MRI*, Magnetic resonance imaging.

sildenafil was characterized by any decrease in lymphatic malformation volume. Lymphatic malformation 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 gadolinium contrast-enhanced images in the axial and coronal planes. All images were sent to an independent workstation with real-time multiplanar reformation capability (Osirix, Pixmeo, Geneva, Switzerland).[12] A senior pediatric radiologist blindly calculated lymphatic malformation 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 lymphatic malformation was calculated on the aggregate of the individual segmentations. The percentage of macrocysts in the lymphatic malformation was determined using baseline MRI examinations. Estimates of microcystic and mixed components were not performed because of the lower accuracy of these estimates with MRI software.

Secondary outcomes included both physician and parent assessments of lymphatic malformation improvement compared with 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 lymphatic malformation at baseline were provided for comparison. A 5-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 lymphatic malformations before 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.

Table I. Baseline demographics and clinical characteristics

	Subjects, N = 7
Male sex, no. (%)	4 (57.1)
Age	
Mean, mo (range)	51.3 (13-85)
Weight at baseline	
Mean, kg (range)	17.0 (9.7-24.2)
LM location, no. (%)	
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, mo (range)	1.1 (0-6)

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

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 lymphatic malformation located in the head/neck, and 1 subject had a lymphatic malformation located in the abdomen. Lymphatic malformation complications before sildenafil initiation included infection (N = 3), hemorrhage (N = 1), and obstruction of anatomical structures (N = 1). Previous lymphatic malformation interventions included surgery (N = 2) and doxycycline sclerotherapy (N = 2). The percentage of macrocysts in each lymphatic malformation is shown in Table II.

Table II. Percent change in lymphatic malformation volume

Subject	Volume of LM, mL		Volume difference, mL	Volume change, %	Macrocystic component, %
	Baseline	End of treatment			
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.

All subjects completed 20 weeks of sildenafil (mean = 22 weeks). Subjects who were unable to complete an MRI at week 20 because of 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 before enrollment (mean = 3.1 months).

Using MRI volume segmentation analysis, 4 subjects had a lymphatic malformation volume decrease (1.0%-31.7%) (Table II). In 2 children (subjects 1 and 6), clinical improvement was noted while on sildenafil despite a lymphatic malformation volume increase (1.1%-3.7%). Before initiating sildenafil, subject 1 had failed auditory tests because of infiltration of the lymphatic malformation in her right ear canal and experienced obstructive sleep apnea and airway occlusion while turning her neck as a result of the mass effect of the lymphatic malformation 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 lymphatic malformation despite the 1.1% increase in lymphatic malformation 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% lymphatic malformation 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 lymphatic malformation volumes had lymphatic malformations with 1.6% and 76.0% of macrocysts, respectively (Table II).

Lymphatic malformations softened and became easily compressible in subjects 1 to 6. The parents and physicians reported improvement in tenseness/texture of the lymphatic malformation, and 5 of 6 subjects reported overall improvement compared with baseline. The parents of subject 4, who had a 31.7% decrease in lymphatic malformation volume, noted that she was more confident with her appearance at the end of the study (Fig 2). At week 20, the lymphatic malformation of subject 5 was soft and its borders were difficult to identify. His parents rated a 50% to 75% improvement in tenseness/texture and a 75% to 100% overall improvement at week 20 compared with 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. Before initiating sildenafil, subject 2 had multiple hospitalizations for acute abdominal pain from lymphatic malformation infections after episodes of flu-like illness. While on sildenafil, he had no episodes of abdominal discomfort or lymphatic malformation 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 because of their impression of improvement in the lymphatic malformation 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 lymphatic malformations.

Softening of the lymphatic malformation appeared to contribute to the symptomatic improvement in 6 subjects. The resolution of life-threatening episodes of sleep apnea, airway obstruction,

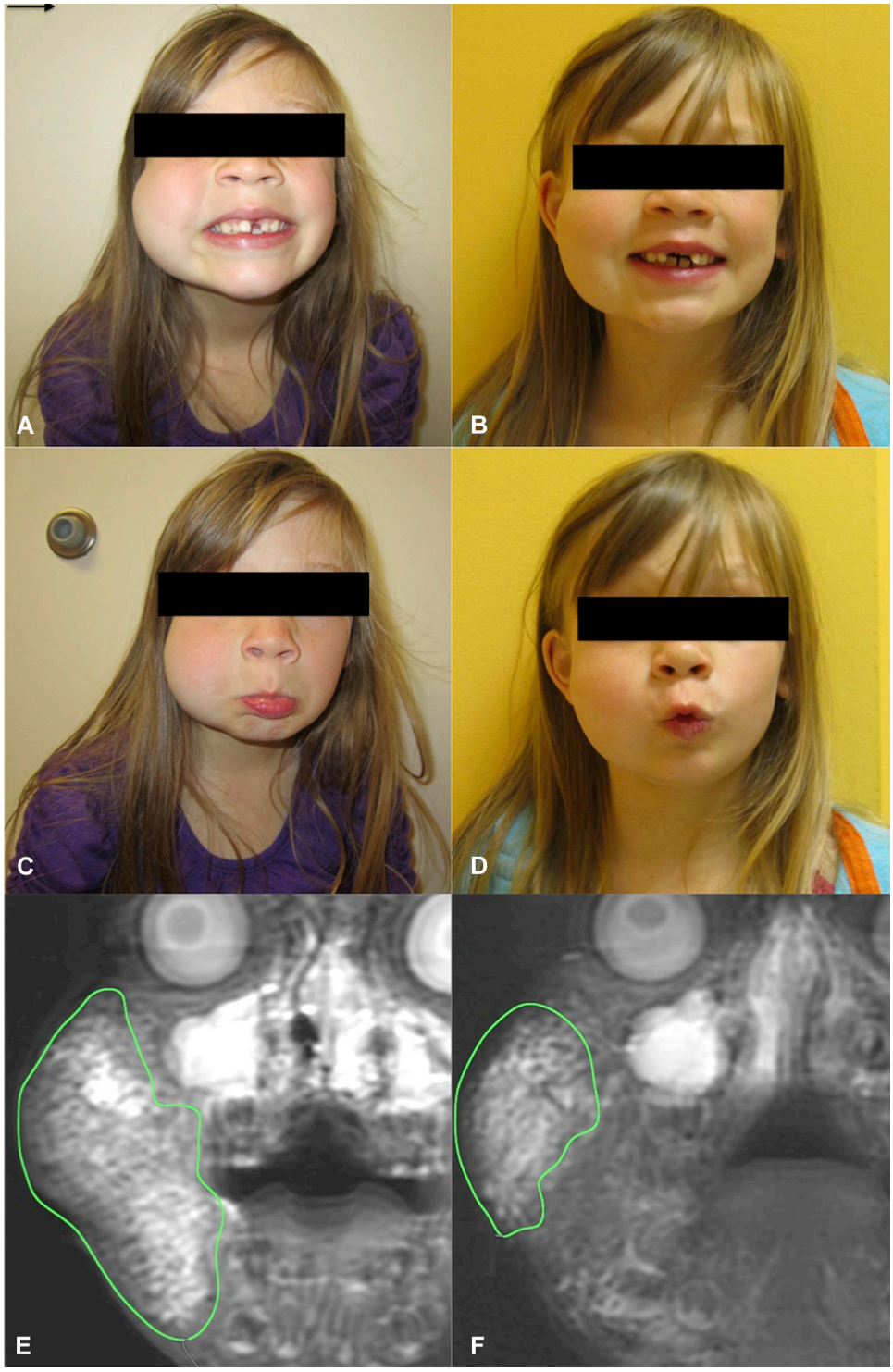

Fig 2. Lymphatic malformation (LM). Photographs of subject 4 at baseline (**A** and **C**) and after 20 weeks of sildenafil (**B** and **D**). Coronal T2-weighted fat-suppressed magnetic resonance images show a microcystic-predominant LM in the left superficial premandibular and premaxillary soft tissues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

and frequent infection was likely secondary to lymphatic malformation softening. The recent use of sildenafil for orbital lymphatic malformations further demonstrates that sildenafil can decrease symptomatic lymphatic malformation swelling.[13] It is unclear why the lymphatic malformation in subject

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 lymphatic malformation, with or without a deeper macrocystic component.

7 continued to expand while on sildenafil. There were no other imaging features of the lymphatic malformation in this subject compared with other patients. Decreased lymphatic malformation volume was observed on sildenafil in both macrocystic- and microcystic- predominant lesions. Therefore, inherent biologic differences other than cyst size may exist in lymphatic malformations that impact response to sildenafil.

The rate of progression of the lymphatic malformations before the initiation of sildenafil is unknown. Several hypotheses about lymphatic malformation progression exist including growth by lymphangiogenesis, excessive fluid secretion, poor drainage, lymphatic aggregation, and cellulitis.[4,14] Sildenafil may slow the growth of the lymphatic malformation. 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 lymphatic malformation may affect the response to sildenafil. It has been suggested that diffuse lymphatic malformations have a greater likelihood of progression than focal lesions.[4] Diffuse lymphatic malformations 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 lymphatic malformations may require a longer treatment course or a higher dose of sildenafil to experience a larger decrease in lymphatic malformation volume. Subjects 4 and 5 had focal lymphatic malformations and responded best to sildenafil based on lymphatic malformation 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 lymphatic malformation 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 lymphatic malformation treatments (Table IV). Subject 4 had 4 sclerotherapy sessions before enrolling in the study and had the best response on sildenafil.

To limit the risks of anesthesia, MRI examinations performed within 6 months before the commencement of sildenafil were accepted to calculate the baseline lymphatic malformation volume. Lymphatic malformations 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 because of MRI scheduling and personal accommodations. We did not identify that slight variations in the duration of sildenafil affected lymphatic malformation volume change. MRI volume segmentation was necessary to quantify changes in lymphatic malformation volume because 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 lymphatic malformations respond best. Optimal duration of treatment and dosage regimen needs to be examined further. Sildenafil may be a potential noninvasive therapeutic alternative for lymphatic malformations. An effective oral medication for treatment of lymphatic malformations would motivate additional research and could lead to further knowledge of the mechanisms underlying lymphatic malformations.

Table IV. Clinical characteristics of 7 subjects

Subject	1	2	3	4	5	6	7
Sex	Female	Male	Female	Female	Male	Male	Male
Age, mo	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 side of 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 premandibular area and premaxillary 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, mo	Birth	Birth	Birth	Birth	Birth	6 mo	2 mo
Previous LM treatment	Surgery (×1)	Doxycycline sclerotherapy (×2)	Surgery (×1)	Doxycycline sclerotherapy (×4)	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/d	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 pretreatment, mL	179.4	1453.7	25.2	62.2	44.8	27.2	243.0
MRI volume posttreatment, 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.

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