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### Title

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### Permalink

<https://escholarship.org/uc/item/9bw1m5t1>

### Journal

Journal of vascular surgery. Venous and lymphatic disorders, 9(1)

### ISSN

2213-333X

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### Publication Date

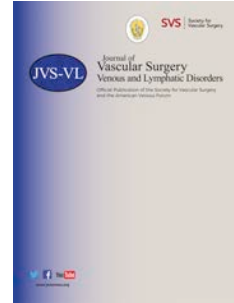
2021

### DOI

10.1016/j.jvsv.2020.04.001

Peer reviewed

# Journal Pre-proof



Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients

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PII: S2213-333X(20)30210-9

DOI: <https://doi.org/10.1016/j.jvsv.2020.04.001>

Reference: JVSV 983

To appear in: *Journal of Vascular Surgery: Venous and Lymphatic Disorders*

Received Date: 5 January 2020

Accepted Date: 2 April 2020

Please cite this article as: K.J. Nelson, P. Antiquera, J.S. Nelson, K.M. Kelly, N. Abi-Jaoudeh, Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in adult and teen patients *Journal of Vascular Surgery: Venous and Lymphatic Disorders* (2020), doi: <https://doi.org/10.1016/j.jvsv.2020.04.001>.

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1 Effect of long-term phosphodiesterase-5 inhibitor use on refractory lymphatic malformations in  
2 adult and teen patients

3

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16

17 Abstract

18 Lymphatic malformations (LM) are rare congenital anomalies. LM are often refractory to  
19 standard treatments including surgical resection, debulking and sclerotherapy. Use of sildenafil, a  
20 phosphodiesterase-5 inhibitor (PDE-5i), for treatment of pediatric LM has been reported with  
21 demonstrated benefit to some patients. This case series reports treatment of three patients (ages  
22 14-37 years) suffering from complicated or refractory LM with low dose oral PDE-5i resulting in  
23 significant clinical improvement.

1

2 Key words: lymphatic malformation, sildenafil, phosphodiesterase-5 inhibitor

3 Author conflict of interest: none

4

5 Lymphatic malformations (LM) are rare congenital anomalies<sup>1,2</sup> and are notoriously refractory  
6 to treatment. Conventional treatment options are invasive and include surgical resection,  
7 debulking and sclerotherapy. Despite these treatments, patients often remain plagued by LM. An  
8 initial report of LM improvement on sildenafil, a PDE-5i, in a pediatric patient undergoing  
9 treatment for pulmonary arterial hypertension<sup>3</sup> prompted early studies involving the use of  
10 sildenafil for treatment of LM in pediatric patients<sup>4,5</sup>. Subsequent studies did not demonstrate  
11 similar success<sup>2,6</sup>. Sildenafil use for treatment of LM has been reported in patients from 12 days  
12 old to 16 years; however, even studies including teen patients had a median age under 10 years<sup>1,2,</sup>  
13 <sup>4,5,6</sup>. The treatment of adult LM patients with sildenafil has not been published.

14 Following IRB approval, patients at a single institution with refractory lymphatic malformations  
15 treated with oral PDE-5i were retrospectively identified and reviewed. Consent to publish was  
16 obtained from each patient and/or from each patient's legal guardians.

17 Patient 1

18 18-year-old woman with congenital microcystic LM of the pelvis with trans spatial involvement  
19 presented to our institution with daily bleeding, oozing, pain and intermittent infection of the LM  
20 at the gluteal cleft (Figure 1a). The patient was prescribed a 10-week course of oral sildenafil  
21 given the severity of her condition. The insurer would not authorize sildenafil, but approved an  
22 alternate PDE-5i, tadalafil 5 mg by mouth taken at bedtime (po QHS). After 3 weeks of PDE-5i,  
23 all bleeding and drainage had resolved. After completion of 10-weeks of PDE-5i, the patient

1 underwent initial sclerotherapy using doxycycline. Four weeks post-treatment, the patient  
2 reported mild oozing of the malformation but decreased tenseness and discoloration. PDE-5i was  
3 again prescribed but denied by her new insurer. The patient underwent 5 additional image-guided  
4 sclerotherapy treatments over 18 months using doxycycline, sodium tetradecyl sulfate and  
5 bleomycin. After each treatment, components would slough and regrow; the malformation would  
6 dry up and then resume mild oozing and bleeding, remaining stable or slightly decreased in size  
7 (Figure 1b). Given diminishing improvement with sclerotherapy and concern for cumulative  
8 radiation dose, appeal for PDE-5i use was resubmitted and approved. The patient began taking  
9 sildenafil 20 mg po QHS. Within 4 weeks, all oozing and bleeding had resolved, pain decreased  
10 and LM appeared smaller. Continued shrinkage of LM was experienced with ongoing use of the  
11 PDE-5i, except for a large, sessile component along the right gluteal cleft. Trial of topical  
12 rapamycin to this area was initiated but resulted in bleeding and oozing and was discontinued.  
13 The patient chose to continue PDE-5i use. The patient has been on continuous PDE-5i use for 35  
14 months with ongoing improvement (Figure 1c). At no time during the course of PDE-5i use has  
15 the patient experienced adverse effects of the drug nor has she experienced genital swelling or  
16 arousal related to taking the drug.

#### 17 Patient 2

18 37-year-old woman with congenital right neck/supraclavicular mixed LM with trans-spatial  
19 involvement presented with worsening right neck and arm pain. The congenital lesion had been  
20 quiescent and was believed to be a lipoma until her first pregnancy, at which time it acutely  
21 enlarged, causing pain and mass effect. The patient was refused surgical resection or debulking  
22 given involvement of the right brachial plexus. Sclerotherapy was performed, followed by a  
23 decrease in lesion size and symptoms for 1 year. When symptoms recurred, the patient

1 established care at our institution and underwent 7 additional percutaneous sclerotherapy  
2 treatments over 6 years using doxycycline and sodium tetradecyl sulfate. Each treatment was  
3 triggered by increased size and mass effect resulting in right arm pain and intermittent right hand  
4 tremor. Alternative treatments were discussed. The patient was started on a PDE-5i (sildenafil 20  
5 mg po QHS) (Figure 2a). At 3 months, the patient reported stable lesion size and no tremor  
6 recurrence. At 5 months, the patient reported decreased size and swelling of the LM. At 20  
7 months, the lesion was further decreased in size and asymptomatic (Figure 2b). Patient has  
8 denied adverse effects of the PDE-5i throughout treatment and denied genital swelling or arousal  
9 related to taking the drug.

#### 10 Patient 3

11 14-year-old male with congenital right neck mixed LM with trans-spatial involvement presented  
12 with bleeding from his LM following initiation of topical imiquimod. The patient's LM was  
13 noticed at 12 months of age, but remained clinically silent until 13 years when it began to  
14 intermittently bleed. The patient was started on topical imiquimod, which caused increased  
15 bleeding, and was then discontinued. Following interdisciplinary evaluation, patient underwent  
16 percutaneous sclerotherapy using doxycycline with subsequent improvement in appearance and  
17 decreased bleeding. Patient and his family desired treatment but wished to avoid repeat  
18 sclerotherapy. After lengthy discussion, the patient was started on a trial of PDE-5i (sildenafil  
19 20 mg po QHS). After 6 weeks, the patient's parents reported a "drastic improvement" in the  
20 malformation. After 5 months of PDE-5i, the LM is asymptomatic and has lightened in  
21 coloration. Patient continues to deny adverse effects of the drug (such as flushing, changes in  
22 vision or hearing, dizziness, nausea) and has not experienced erection related to taking the drug.

#### 23 Discussion

1 All 3 patients in our series presented with complications of their LM. Two were refractory to  
2 traditional treatments, and two demonstrated acute worsening with topical immune modulator  
3 treatment. Initial improvement with low dose PDE-5i was seen between 3 weeks and 5 months.

4 All patients experienced sustained improvement over time with use of PDE-5i. Duration of  
5 continuous PDE-5i for 2 patients has significantly exceeded treatment durations previously  
6 reported for pediatric LM<sup>1, 2, 3, 4, 5, 6</sup>.

7 PDE-5i lead to smooth muscle relaxation in blood vessels causing dilation and may similarly  
8 affect lymphatic vessel smooth muscle. The mechanism by which PDE-5i act upon lymphatic  
9 malformations is extrapolated from in vitro study in which a relationship between nitric oxide  
10 and lymphatic vessel growth via production of cyclic guanosine monophosphate (cGMP) was  
11 demonstrated<sup>7</sup>. cGMP mediates lymphatic endothelial cell proliferation<sup>7</sup>. PDE-5i prevents  
12 degradation of cGMP by inhibiting PDE-5, prolonging the presence of cGMP which may  
13 facilitate lymphatic vessel growth and improve drainage of lymphatic malformations<sup>7</sup> (Figure 3).  
14 Further investigation is needed.

15 PDE-5i have been commercially available since 1998<sup>8</sup>. Chronic use of PDE-5i has not  
16 demonstrated chronic side effects although data is limited<sup>8</sup>. Side effects related to sildenafil use  
17 for pediatric LM have been limited and mild, most commonly involving flushing, dizziness and  
18 nausea.

19 The treatment of non-pediatric LM population with sildenafil has not been published. The  
20 prescription of PDE-5i in a sexually maturing or mature patient raises concern for side effects  
21 including unwanted erection or genital swelling/arousal. For this reason, the patients in this  
22 series were treated with low-dose PDE-5i at bedtime, with significantly lower dosing compared  
23 to the pediatric studies published to date<sup>1,2,4,5,6</sup>. In our series, there were no reports of side effects

1 with the low dose regimen which may be related to the dose or to the bedtime administration of  
2 the medication. Despite the low dose, all patients demonstrated significant clinical response.  
3 Based upon the relatively benign safety profile, the clinical response and lack of side effects, all  
4 patients have elected to continue PDE-5i use for now. Given paucity of data on long-term PDE-  
5 5i use and lack of randomized controlled trials on treatment of LM with PDE-5i, caution with  
6 use of PDE-5i for treatment of LM and careful patient screening are needed.

7

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9

1 Figure Legend

2

3 Figure 1. Cutaneous component of the congenital microcystic lymphatic malformation: 1a.

4 Appearance at initial presentation, with evidence of ongoing bleeding and oozing; 1b.

5 Appearance after 6 sclerotherapy sessions, with stable or slightly decreased size of the majority

6 of the malformation and evidence of decreased bleeding and oozing; 1c. Appearance after 35

7 months of PDE-5 inhibitor use with decreased size of the malformation, lightened coloration and

8 resolution of all bleeding and oozing.

9

10 Figure 2. Contour abnormality of the right lower cervical region related to underlying mixed type

11 lymphatic malformation: 2a. Appearance following 8 sclerotherapy sessions; 2b. Appearance

12 after 20 months PDE-5 inhibitor use with decreased contour abnormality and decreased

13 displacement of the patient's necklace.

14

15 Figure 3. Potential mechanism of action for PDE-5 inhibitors on lymphatic malformations: Nitric

16 oxide interacts with the enzyme guanylate cyclase to enable conversion of GTP to cGMP; PDE-

17 5i prevents breakdown of cGMP by inhibiting PDE-5, resulting in prolonged activation of

18 cGMP; cGMP may then cause smooth muscle relaxation in lymphatic vessels decreasing

19 pressure within lymphatic structures and may contribute to generation of new lymphatic vessels.

20 GTP= guanosine triphosphate; cGMP= cyclic guanosine monophosphate; GMP= guanosine

21 monophosphate; PDE-5= phosphodiesterase; PDE-5i= phosphodiesterase-5 inhibitor.









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