Belshe when our study began. However, in a previous study comparing MF59-ATIV and Sanofi Pasteur TIV (Vaxigrip) in children 6 to 35 months of age, we showed that the ATIV was also significantly more immunogenic for all three viral subtypes than the TIV. We disagree that the efficacy of 43% (95% confidence interval [CI], 15 to 61) for TIV in children under the age of 72 months in our trial was inordinately low. One meta-analysis showed no TIV studies in children 2 to 17 years of age with a design that was sufficiently rigorous to be included, and another meta-analysis concluded that TIV had a 59% efficacy (95% CI, 41 to 71) in healthy children under the age of 16 years, with no efficacy in those 6 to 24 months of age.

We agree with Heikkinen and Heinonen that the appropriate TIV dose may not be reflected in current licensed pediatric indications. In their study, the vaccine effectiveness of 0.5 ml of TIV was 66% (95% CI, 29 to 84) against all circulating influenza strains in children under the age of 36 months. This finding falls between the efficacies of 43% (95% CI, 15 to 61) for TIV and of 86% (95% CI, 74 to 93) for ATIV in our study, in which 0.25-ml doses were used in children under the age of 72 months.

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Since publication of their article, the authors report no further potential conflict of interest.


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Sildenafil for Severe Lymphatic Malformations

**TO THE EDITOR:** Lymphatic malformations are uncommon congenital vascular anomalies that can cause complications including obstruction of vital organs and their function, recurrent infection, and disfigurement. Current procedural treatments are only partially successful, and lymphatic malformations often recur. We report marked regression of lymphatic malformations in three children after treatment with oral sildenafil.

A 10-week-old girl presented with a congenital, nonpulsatile, violaceous, nodular plaque causing massive enlargement of the right chest and arm. A scan obtained with magnetic resonance imaging (MRI) revealed microcystic venolymphatic malformation with intrathoracic extension (Fig. 1A). At 5 months, congestive heart failure developed. An echocardiogram showed pulmonary hypertension without congenital anomalies. Despite initial improvement after treatment with conservative measures, the patient’s cardiorespiratory condition worsened. At 9 months, cardiac catheterization confirmed the presence of idiopathic pulmonary hypertension, and sildenafil was initiated. The malformation gradually diminished, and 4 months later a thin, blue plaque and redundant tissue were seen. A subsequent MRI of the heart confirmed the presence of only minimal residual lymphatic malformation (Fig. 1B).
On the basis of this observation, a pilot study was approved by the institutional review board at Stanford University. Two children with disabling lymphatic malformations received sildenafil for 12 weeks.

In Subject 1, a 12-month-old boy, the lym-
phatic dysfunction involved the orbit and upper eyelid and obstructed visual input. Although improved eye opening was noted after 3 weeks, debulking was performed because of concerns about amblyopia. At the study’s end, the child’s ability to open the affected eye had increased by 25%. Tissue enlargement recurred after sildenafil was discontinued. Subject 2, a 15-month-old girl, had three large lymphatic malformations and had undergone sclerotherapy with partial improvement (Fig. 1C and 1D). After administration of a 12-week course of sildenafil, the malformations had diminished by about 75%, with the malformation on her back appearing deflated, leaving sagging skin (Fig. 1E). Sildenafil was stopped, and mild enlargement was noted 4 weeks later (Fig. 1F).

Neither child had significant adverse effects from treatment. Both families elected to continue administration of sildenafil after study completion.

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. The drug has been approved for the treatment of pulmonary hypertension in adults; it is used off-label in children with pulmonary hypertension and appears to be safe and effective.

Lymphatic malformations are hypothesized to develop from primitive lymphatic sacs that arise from mesenchyma or embryologic endothelial networks. The contraction of thickened muscular linings may increase intramural pressure and cause cystic dilatation. A potential explanation for the therapeutic effect seen in this series is the relaxation of smooth muscle followed by cystic decompression. Alternatively, relaxation may allow secondary lymphatic spaces to open, or sildenafil may normalize lymphatic endothelial dysfunction.

The observations described suggest that sildenafil represents an encouraging, propitious treatment for lymphatic malformations, used as monotherapy or with other treatments. A double-blind, placebo-controlled trial is under way.

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