Combination of treprostinil with sympathectomy and vascular reconstruction to treat recurrent digital ulcer disease

Sirs,

Digital ulceration is an obliterative vasculopathy associated with substantial morbidity (1). We present two patients with critical digital ischaemia treated with intravenous (IV) treprostinil and surgery, followed by maintenance therapy with oral treprostinil to prevent recurrence.

Case 1. A 50-year-old female with limited systemic sclerosis (anti-nuclear antibody (ANA) 1:640 with centromere pattern) presented with acute digit-threatening necrotic ulcers of her right third finger. Six months prior, she had required partial amputations of her 2nd and 5th right digits and had sympathectomy of the right ulnar artery. Ulceration recurred despite aspirin, clopidogrel, amlodipine, pentoxifylline, and bosentan. She was admitted for IV treprostinil with right snuff box, palmar arch, and common digital sympathectomy. She was discharged on oral treprostinil (Table I) without further amputations or hospitalisation.

Case 2. A 21-year-old female with diffuse systemic sclerosis (ANA 1:640 and anti-topoisomerase I–4.5) presented with left thumb and right third digit-threatening ulcer disease. She was admitted for IV treprostinil and continued cilostazol and tadalafil; she was discharged on oral treprostinil. She had recurrent progressive digital ulceration after an injury and required IV treprostinil to salvage the digits before transitioning back to oral treprostinil. Due to progressive gangrenous ulcerations on her bilateral first, third, and fourth digits she was admitted for IV treprostinil (Table I). Arteriogram showed thrombosis of the ulnar arteries bilaterally. She underwent left ulnar artery reconstruction with an arterial graft and sympathectomy of the common digital vessel to middle and ring fingers. New ulcerations on her right third and fifth digits developed 10 months later which prompted reconstruction of ulnar artery alongside sympathectomy of the right radial and palmar arch. She has not had recurrent ulceration on either hand despite reduced oral treprostinil.

These cases highlight the strategy of using treprostinil in concert with surgical approaches to rescue critical digital ischaemia and maintain perfusion, preventing recurrent ulceration in systemic sclerosis. We highlight arterial occlusion amenable to reconstruction as an important source of morbidity and a therapeutic opportunity that is often overlooked. This often involves the ulnar artery, presumably due to the anatomy, as it is more likely to be compressed by thickened forearm fascia in its course through Guyon's canal.

Digital ulcerations are common (~50%) in systemic sclerosis. Despite anti-platelet and oral vasodilators, 4.8% require amputation (1); prostanoids are reserved for recurrent or refractory ulceration (2). Digital sympathectomy is an efficacious option, which improves wound healing (3). Resolution of ulcers were seen more commonly after treatment with sympathectomy and bypass when compared to sympathectomy alone (4). Despite this data, sympathectomy (5) and vascular reconstruction are rarely performed.

Treprostinil (6) and iloprost (7) are prostacyclin analogs that have been used to salvage digits, but the IV format limits their use. Treprostinil has an oral form and despite it improving digital perfusion (8), it did not prevent recurrent ulceration compared to placebo (9). However, discontinuing oral treprostinil was associated with an increase in digital ulcer recurrence (10). This suggests that oral maintenance therapy may be valuable once ulcers heal. No previous study evaluated combination treprostinil and sympathectomy/reconstruction to prevent future ulcer disease.

Given the pain, disability, and health care utilisation associated with digital ulceration, better treatment strategies are needed to improve and maintain perfusion. After conservative therapy fails, we recommend a multidisciplinary approach using prostanoids and vascular reconstruction. We found utilising treprostinil (parenteral followed by oral) in combination with extensive sympathectomy (with or without arterial reconstruction) leads to improved and sustained perfusion. Further studies are needed to evaluate this strategy in reducing recurrent ulcerative disease.

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Table I. Treprostinil therapy used to treat digital ulcer disease.

Hospital Day	Patient 1	Patient 2		
	Hospitalisation	Hospitalisation - 1	Hospitalisation - 2	Hospitalisation -3
0	IV treprostinil initiated at 4 ng/kg/min	IV treprostinil initiated at 2 ng/kg/min	IV treprostinil initiated at 4 ng/kg/min	IV treprostinil initiated at 4 ng/kg/min
2-4	Treprostinil was titrated up to 10 ng/kg/min with improvement in pain and perfusion.	Treprostinil was titrated up to 10 ng/kg/min with improvement in finger pain and perfusion.	Treprostinil was titrated up to 12 ng/kg/min with improvement in pain and perfusion.	Treprostinil was titrated up to 12 ng/kg/min with improvement in pain and perfusion.
8-12		Treprostinil was transitioned to oral 1.25 mg every 8 hours.	Treprostinil was transitioned to oral 6 mg every 8 hours.	Treprostinil was transitioned to oral 6 mg every 8 hours.
14-16	IV treprostinil was increased to 12 ng/kg/min with improved pain and perfusion. It was transitioned to 2 mg every 8 hours.			

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