Venous Leg Ulcer Clinical Trials: Separating Promise From Proof

The current landscape of clinical trials for VLUs is promising but highlights the need for improved trial design and more definitive evidence.

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Venous leg ulcers (VLUs) account for 70% to 90% of all chronic leg ulcers, imposing a heavy burden on both patients and our health care system globally. High recurrence rates, slow healing, and complex pathophysiology demand a multifaceted approach to treatment. The EVRA trial was a pivotal landmark clinical trial demonstrating that early endovenous ablation led to faster ulcer healing and complete healing compared to nonintervention.[1] This clinical trial changed the landscape of early endovenous treatment of VLUs.

We currently have an expansive tool kit to manage VLUs, from innovative surgical techniques to comprehensive wound care, and the current state of clinical trials for VLUs reveals a landscape with some promising developments. These trials will be essential to advancing care and will be key for practicing evidence-based guidelines and standardizing optimal treatment for all affected patients. This article provides a brief summary of trials that are currently underway.

SUPERFICIAL VENOUS INTERVENTIONS: THE RISE OF NONTHERMAL ABLATION

Endovenous ablation has long been a cornerstone of VLU treatment, targeting venous hypertension and enhancing ulcer healing.[1] While endothermal ablative techniques remain standard (eg, radiofrequency ablation, endovenous laser treatment), Spectrum—a single-arm, prospective study assessing VenaSeal (Medtronic) cyanoacrylate ablation in patients with VLUs—demonstrated noninferiority to thermal ablation, with an 81.3% ulcer healing rate and 83% freedom from ulcer recurrence at 1 year.[2]

The VIEW-VLU clinical trial treated refluxing great saphenous veins and/or anterior saphenous veins in patients with VLUs with 1% polidocanol microfoam. Wound healing rates, wound closure after treatment, and time to wound healing were measured. By 12 weeks, over half of the wounds treated were healed. Quality-of-life measures also significantly increased positively in many of these patients. This data from a phase 4 registry of VLU patients show promising wound healing rates and low recurrence rates once healed, especially in challenging patients.[3]

Cyanoacrylate glue and 1% polidocanol have the advantage of treating the entire length of refluxing saphenous vein, without a risk of thermal nerve injury in the distal calf. Although treating the entirety of the diseased vein is thought to enhance healing and prevent recurrence, robust randomized controlled trials (RCTs) are still necessary to validate this approach.

DEEP VENOUS INTERVENTIONS: FILLING THE EVIDENCE GAP

For patients with postthrombotic syndrome (PTS) and VLUs, iliac vein stenting is increasingly common. Yet, strong evidence supporting its use is lacking, and there continues to be a lack of consensus on when intervention, especially with stenting, should be used for patients with PTS. Most clinical trials of venous stenting do not randomize between stenting and no stenting in the acute and chronic setting. In addition, most current guidelines for stenting are based on clinical practice rather than RCTs.

Enter the C-TRACT trial, a multicenter RCT funded by the National Institutes of Health and National Heart, Lung, and Blood Institute, evaluating iliac vein stent placement to reduce the severity of PTS, including in patients with active VLUs.[4] While retrospective data have suggested stents reduce venous hypertension and improve ulcer healing, C-TRACT aims to provide level 1 evidence, answering

critical questions about durability, cost-effectiveness, and patient selection. Patients with PTS are being randomized in a 1:1 ratio of intervention or no intervention treatment groups. Early insights could definitively reshape guidelines for deep venous disease management and affect the debilitating life impact of patients with PTS.

The rationale and design of the DEFIANCE trial is similar, randomizing patients to either mechanical thrombectomy versus anticoagulation alone for iliofemoral deep venous thrombosis.[5] Approximately 300 patients with unilateral iliofemoral deep vein thrombosis with symptoms duration of < 12 weeks will be randomized. Postthrombotic symptoms, including patients with subsequence VLUs, will be followed, and thus, evidence from this trial may not necessarily support "treatment" of VLUs, but rather early deep venous intervention for "prevention" to VLUs.

Direct surgical deep venous valve reconstruction has not been the focus of innovative technology in recent decades, with increased attention mainly turned to decreasing venous hypertension by treating superficial and deep pathologies. However, the SAVVE trial investigated VenoValve (enVVeno Medical), a pivotal deep venous device for improving venous reflux in patients with VLUs. This bioprosthetic valve is placed in the femoral vein and aims to improve deep venous reflux in patients with advanced disease without superficial reflux or iliac vein obstruction. The prospective, multicenter SAVVE trial evaluated the safety and efficacy of the bioprosthetic valve and demonstrated significant clinical improvement in quality of life and ulcer healing at 1 year. At 1-year follow-up, all VLUs with a duration of < 1 year prior to implantation had healed and 89% of VLUs with a duration of > 1 year had healed.[6] The VenoValve is currently implanted surgically, but a percutaneous method of introduction is currently being investigated. Percutaneous delivery will be crucially advantageous for patients with already compromised skin integrity.

BIOLOGIC AND TOPICAL THERAPIES: TARGETING THE WOUND BED

The treatment landscape for VLUs is also evolving with novel biologic and topical therapies that target the underlying pathophysiology of chronic wounds. Leading this effort is the VALUE trial, a phase 3 multicenter study evaluating EscharEx (MediWound), a bioactive debridement agent designed to promote granulation and reduce bacterial load. Patients will be randomized to either EscharEx or placebo, with eight daily applications over a 2-week period followed by 10 weeks of standardized wound care, with the goal of reducing biofilm burden and accelerating healing.[7]

Another promising therapy is the intact fish skin graft from Kerecis. The fish skin, derived from wild Atlantic cod, has shown improved healing rates in one of the largest RCTs on diabetic foot ulcers. In the study, patients with diabetic foot ulcers were randomized to standard-of-care treatment with and without intact fish skin. The intact fish skin treatment group demonstrated significantly higher healing rates compared to standard wound care, even on extensive wounds with exposed bone or tendon.[8] Its omega-3–rich extracellular matrix appears to modulate inflammation and support tissue regeneration. A follow-up observational study is underway assessing long-term durability in patients from the THOR RCT with closed VLUs, a critical factor given VLU's high recurrence rates.[9]

CLEANVLU, a phase 2a trial of Aurase wound gel (SolasCure), is investigating an enzymatic approach to improve microcirculation and breakdown fibrin cuffs that are characteristic of venous disease.[10] CLEANVLU2, an additional phase 2 clinical trial, enrolled its first patient earlier this year.[11] The enzyme investigated in both trials is tarumase, which is cloned from maggots and targets collagen and elastin debridement to increase wound bed preparation. The safety and tolerability of increasing doses are currently being investigated for VLUs, and early data suggest potential to enhance oxygen diffusion and nutrient delivery to the wound bed.[12] In addition to other standard methods to decrease venous hypertension, this adjuvant topical therapy may accelerate wound healing further.

LASER INNOVATION

Using low-level laser therapy on VLUs as an adjunctive therapy to promote wound healing has had mixed results. The laser aims to stimulate healing and reduce inflammation.[13] The anti-inflammatory effect is particularly important, as changes to the venous system cause significant inflammation within the skin, ultimately leading to skin breakdown. RCTs have shown that specific low-level lasers can potentially promote healing by increasing collagen synthesis, enhancing angiogenesis, and, perhaps most importantly, reducing inflammation. Some studies also have shown reduction in pain associated with VLUs. However, the level 1 evidence available were of small sample size, lack standardization of treatment protocol, and had high risk of bias.[14,15] Appropriately designed trials are needed to further investigate its potential benefits.

High-intensity laser therapy on the wound bed to promote VLU wound healing is also being investigated in an RCT.[16] Previously, high-intensity laser therapy has been used on chronic refractory wounds with promising results as an adjuvant to standard wound

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care.[17] However, given the varied wounds of different etiologies and limited number of patients enrolled, subgroup analysis specific to VLU patients could not be performed in this study. A more recent clinical trial focused on VLU patients, receiving either laser therapy 3 times a week for 8 weeks with wound care or wound care alone.[18] Questions remain about accessibility and cost-effectiveness in real-world settings.[18]

ADJUNCTIVE THERAPIES: THE ROLE OF PENTOXIFYLLINE

The ESPECT trial, a multicenter RCT in China, is evaluating the role of pentoxifylline, an anti-inflammatory agent used as an adjunct to compression therapy in patients with VLUs. As noted previously, VLUs have a high burden of sustained inflammation from increased venous hypertension—a hallmark of their chronicity. In this clinical trial, all patients will receive 400 mg of pentoxifylline twice daily or placebo for 24 weeks, with the primary outcome of wound healing rate at 12 weeks. If successful, this low-cost oral therapy could become a valuable tool in combating the chronic inflammation that perpetuates and sustains VLUs.[19]

CHALLENGES AND THE PATH FORWARD

Despite advancements, VLU trials face persistent hurdles. Blinding difficulties, inconsistent endpoints, and underpowered studies plague many RCTs. Diverse patient recruitment is necessary for real-world applicability of results but remains challenging often due to socioeconomic barriers. Moving forward, we must prioritize standardized outcome measures, long-term durability of results, and inclusive trial designs to ensure findings translate into real-world benefits.

CONCLUSION: A NEW ERA IN VLU CARE?

The current state of clinical trials for VLUs highlights the need for improved trial design and execution to enhance the reliability of findings. Innovations like VenaSeal, iliac vein stenting, and bioactive wound therapies are expanding our tool kit, but definitive evidence remains scarce.

As research progresses, a personalized multimodal approach combining endovascular intervention, advanced wound care, and pharmacotherapy may finally turn the tide against this debilitating resource-intensive condition. Clinicians must balance optimism with scrutiny, awaiting the robust data needed to refine best practices. ■

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