ROUNDTABLE DISCUSSION

Tailored Approaches to Venous Ulcers

Experts discuss the EVRA trial and its applicability to practice, diagnosis of venous ulcers, wound care management and interaction with wound care specialists, treatment of concomitant deep and superficial disease and perforators, and future directions.

WITH MARK J. GARCIA, MD, MS, FSIR, FACR; MANJIT GOHEL, MBChB, MD, FRCS, FEBVS; AND RAGHU KOLLURI, MD, RVT, RPVI

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Mr. Gohel, as an investigator in the EVRA trial that was presented at Charing Cross 2018 and published in *The New England Journal of Medicine*,[1] how would you summarize the key findings?

Mr. Gohel: The aim of the EVRA study was to establish whether prompt endovenous ablation of superficial reflux can improve venous ulcer healing. In a pragmatic randomized clinical trial, 450 patients with CEAP (clinical, etiology, anatomy, and pathophysiology) C6 disease were recruited from 20 vascular centers in the United Kingdom. All patients were treated with compression therapy and were randomly allocated to undergo either early endovenous ablation (performed within 2 weeks of randomization) or deferred endovenous ablation (performed once the ulcer had healed or after 6 months). The endovenous treatment modality and strategy was left to the discretion of the treating clinician,

and the primary outcome measure was time to ulcer healing.

The main finding of the trial was that the median time to ulcer healing was significantly shorter for patients randomized to early endovenous ablation (56 vs 82 days). The 24-week healing rates were 85.6% in patients in the early intervention group compared to 76.3% in the deferred intervention group. Ulcer-free time to 1 year was also superior in the early intervention group (median, 306 vs 278 days). Overall, the results of the EVRA study strongly supported a strategy of prompt ablation of superficial reflux in patients with venous ulceration.

How might the EVRA data reinforce or modify your delivery of endovenous intervention?

Dr. Kolluri: We work with our podiatry colleagues in comanaging our venous leg ulcer (VLU) patients. Most of our Critical Limb Wound Center patients undergo initial evaluation and assessment for reflux and obstruction, just as they undergo initial arterial assessment for other lower extremity wounds. The patients are then offered endovenous therapy as required. However, the key hurdle is the insurance payor requirement of a minimum of 6 to 12 weeks of conservative/compression therapy before the endovenous therapies are approved. So, although EVRA trial results have shed new light on the importance of eliminating early venous reflux, modifications in practice require a change in insurance payor policies. Unless that happens, EVRA results are not going to change care delivery for VLU patients.

Dr. Garcia: The EVRA data reinforce what we already believed and personally practiced. VLUs occur secondary to venous hypertension transmitted to the skin, and reducing these forces will aid in ulcer healing. Early intervention to reduce hypertension is key to early healing and prevention of recurrence. The question still being debated is whether insufficiency or central iliofemoral disease should be treated first.

Mr. Gohel: In many health care settings around the world, the management of chronic venous ulceration is primarily focused on wound care rather than addressing the underlying pathophysiologic causes of ulceration. The EVRA study findings demonstrated an unequivocal benefit for early endovenous ablation in patients with venous ulcers. These data should motivate clinicians to ensure that early duplex assessment and prompt endovenous interventions are core components of leg ulcer care pathways. Closer working relationships between primary and secondary care clinical teams are essential to optimizing the care of leg ulcer patients.

Drs. Garcia and Kolluri, to what degree do you think the EVRA data are currently applicable in the United States (ie, any considerations/roadblocks with reimbursement)?

Dr. Garcia: The data should be applicable to the United States population, as the hemodynamics in venous ulceration pertain to humans across the globe. I would hope that the results would not only be applicable but accepted by the Centers for Medicare & Medicaid Services and third-party payors across all populations.

Dr. Kolluri: The entirety of the EVRA results are applicable in the United States. However, it is important to understand that the data set included VLUs that are around 3 months' duration on average and < 8.2 cm in diameter. We don't have data on the larger and more recalcitrant ulcers. As previously mentioned, the key hurdle is the preapproval process. There needs to be a push from vascular societies in the form of revised guidelines to encourage early reflux elimination in patients with VLUs, and subsequently, local coverage determinations and preapproval requirements must change to conform to the contemporary evidence-based science.

Do you believe that the data will affect guidelines and referral patterns in the United States?

Dr. Garcia: I think there is a strong chance that the data will positively affect the guidelines. *The New England Journal of Medicine* is a strong publication, particularly among primary care physicians. Although referral patterns are a more local issue for the interventionalist, I believe disseminating the data to our potential referring physicians, extenders, and wound care clinics is critical to having the data accepted and implemented into an ulcer treatment algorithm.

Dr. Kolluri: To speculate on the potential change in the referral pattern, one must understand the current referral pattern. Most wound care specialists did not believe that saphenous reflux elimination would help in VLU healing based on the ESCHAR trial results. Therefore, it is not uncommon for us to see patients several months after the onset of a VLU. Most patients would have spent that time in the wound centers. Almost all of them would be seeing wound care specialists weekly to receive wound care, debridement, and compression therapy. Application of expensive skin substitutes is also a highly prevalent practice and is incentivized in the United States. Wound care professionals must be educated about the results of the EVRA trial, and guidelines must change to incorporate early referral to vascular specialists. It's a matter of time.

How do you properly diagnose a venous ulcer and distinguish it from other causes of lower extremity ulceration? How do you approach patients with ulceration secondary to central venous hypertension (eg, congestive heart failure, cor pulmonale)?

Mr. Gohel: Despite the prevalence of the problem, a widely accepted definition of venous ulceration does not exist. In our unit, we favor a pragmatic and relatively simple approach to leg ulcer evaluation. The clinical history can give a strong indication of the likely ulcer etiology, and inspection of the ulcer and surrounding skin can guide the clinician toward the cause. The initial priority is to exclude significant arterial disease, using ankle-brachial index (ABI) assessment, which can be performed in the community. If the ABI is normal (> 0.8), the patient can be started on compression therapy. Venous duplex ultrasound imaging is primarily used to identify treatable superficial reflux but also to assess the deep venous system. In specific clinical situations, additional investigations such as proximal deep venous imaging or wound biopsy may be needed.

In our experience, chronic venous hypertension is a significant factor in most chronic leg ulcers and efforts to reduce venous hypertension may be beneficial, even when other pathologies may be present. Patients with central causes of venous hypertension (eg, heart failure) present a significant challenge. However, the principles of management remain the same (ie, diagnose and address the cause of venous hypertension, in addition to compression therapy).

Dr. Kolluri: This is a fantastic question, but a loaded one. VLUs, unlike arterial ulcers, present in several different morphologies. To diagnose a particular ulcer as an atypical presentation of VLU or an entirely different etiology, one has to go back to the basics of history and physical examination skills and also pay careful attention to the surrounding dermatologic manifestation. It is also important to get a good history regarding other systemic complaints. Finally, if one is unsure about the etiology, a wound biopsy and in-person discussion with the dermatopathologist are key.

In my opinion, intravenous hypertension at the venular level could be a manifestation of pathology ranging from saphenous or deep vein reflux, obstruction, or elevated central venous pressure. Again, thinking out of the "vascular box" and considering all causes of edema are vital to the management of VLUs. At OhioHealth, we are fortunate to have our vein center, wound center, and advanced heart failure center housed on the same floor, and some patients see all three specialists on the same day to get optimal holistic care. Timing of endovenous therapy is individualized, based on the severity of right heart failure, response to medical therapy for the heart failure, tolerance to compression therapy, and wound healing.

Dr. Garcia: The first step to diagnosing a VLU is evaluation via history and physical examination. The location of the ulcer as well as the appearance of the ulcer and surrounding tissue greatly influence my interpretation of whether the ulcer is related to venous hypertension. Venous pathology will often be accompanied by irregular margins, shallow ulcer, edema, weeping wounds, skin discoloration, induration, or lipodermatosclerosis. Arterial wounds more typically are deep and appear "punched out"; have regular margins; are dry without exudate; skin is cool to touch, pale, or cyanotic; and occur in the foot and phalanges.

Once the one-on-one evaluation is completed, I will order the test I believe to be appropriate, most commonly a venous Doppler study with insufficiency evaluation, and request that it be performed in the standing position. Concerning central venous pathology, if the etiology is truly central, the signs and symptoms related to venous hypertension will affect both legs rather than unilateral findings, even if the ulcer is only seen in one limb. I look at the common femoral waveforms on the Doppler study to see if both common femoral veins are affected (monophasic) or if it is unilateral to the side of the ulcer.

Finally, I routinely perform venography with intravascular ultrasound (IVUS) evaluation of the iliofemoral segments and inferior vena cava. In patients with venous ulcers, I most often see central venous (iliofemoral) lesions with or without insufficiency. These patients cannot be evaluated with anything less than IVUS, as venography is often unremarkable. IVUS is the only way to accurately identify reverse tapering of the iliofemoral veins, which can lead to venous hypertension and associated sequelae.

What referral networks do you have set up for nonvenous, nonarterial ulcerations?

Dr. Garcia: We have a very active wound care clinic in the hospital that refers many of these patients to the practice for a more in-depth evaluation.

Dr. Kolluri: Most existing referrals for the rarer etiology ulcers come from either primary care doctors or podiatrists.

What is the day-to-day role of the wound care clinic/specialist in wound management strategies for the patients in your facility? What is the preferred wound management strategy?

Dr. Garcia: Our wound care specialists are directly engaged and play an important role in the management of all ulcer patients and follow the Healogics guidelines and protocols for wound care management.

Mr. Gohel: Wound care and tissue viability specialists are highly skilled professionals with much to offer patients with chronic venous ulceration. However, wound care should not be delivered in isolation, and efforts should be made to identify and address the underlying pathophysiologic causes of venous hypertension. On a day-to-day basis, wound care and tissue viability teams have an important role in managing complex wounds with novel technologies. For most patients with chronic venous ulcers, simple nonadherent dressings are the preferred wound management strategy.

Dr. Kolluri: Wound care specialists are the primary caregivers for patients with wounds. They see the patients on a weekly basis, and the wound care strategy depends on the etiology of the wound.

In what ways do interventional and wound care specialists interact and share responsibilities?

Dr. Kolluri: Podiatry and nursing colleagues play a critical role in our Critical Limb Wound Center. Our vascular team's goal is to identify the underlying vascular etiology within the first couple of visits and provide adequate care. Once the vascular interventional or surgical care is provided, we communicate with our podiatry colleagues and refer the patient back to them for longitudinal, weekly wound care. We are reconsulted if the wounds do not heal as expected, if healing is stalled, or if the wounds are becoming larger.

Dr. Garcia: When opening up my new practice, I initially introduced myself to the wound care team and clinic and offered my services in helping them evaluate and treat this patient population. We have just recently instituted a multidisciplinary wound care review board to discuss algorithms and treatments and to review difficult cases to hopefully enhance wound healing.

Mr. Gohel: All health care professionals involved in the management of chronic wounds should strive to work as part of multidisciplinary teams to deliver holistic, evidence-based care. Joint clinics, combined care pathways, and cross-discipline events and learning activities may all help promote shared patient care.

In patients presenting with both deep and superficial disease, which do you treat first? Do you employ a staged or simultaneous approach, and what factors guide these decisions?

Dr. Garcia: In patients with both deep and superficial disease, I first treat the deep venous disease in a staged approach, because I believe that no matter what you do to treat the superficial disease, if deep disease is persistent, it will often continue to produce venous hypertension and delay healing or resolution of a patient's clinical presentation. Additionally, I have seen patients successfully ablated who have had recanalization of their superficial veins from central deep venous obstructive pathology. In many of my patients, this approach has successfully resolved or significantly reduced their sequelae to a point where the concomitant superficial disease does not need to be treated. I will only treat the superficial disease once the treatment of the deep disease has failed to resolve the situation. Treating the deep pathology first is my approach, particularly in those with known chronic deep vein thrombosis (DVT).

Mr. Gohel: The treatment of patients with mixed superficial and deep venous disease (reflux and occlusive) presents a common and difficult challenge. To guide intervention, a detailed clinical assessment is essential, supported by appropriate venous investigations. Duplex ultrasound is the mainstay of venous investigation, but additional venous imaging (eg, CT venography, magnetic resonance venography, venography, IVUS) or physiologic assessments such as photoplethysmography may be useful.

The aim is to be able to identify the dominant factor causing venous hypertension. When there is significant venous outflow obstruction in addition to venous reflux, we generally address the obstructive component first before ablating the superficial reflux. In patients with multifactorial venous hypertension, effective compression therapy is also a core component of management.

Dr. Kolluri: Although a high prevalence of venous obstruction is reported in patients with VLUs, there are no level 1 data that support VLU healing with relief of the obstruction. Similarly, we don't have level 1 data with respect to the management of combined reflux and obstruction and the timing of the therapy. In our practice, we do not provide simultaneous therapy, and in my opinion, this is not necessary. The disease process is chronic, and there is no need to "hurry up." Plus, in the United States, health care expenses increase if the superficial ablative therapies are performed in the inpatient cath lab setting.

The results of the EVRA trial showed that superficial venous interventions alone without relief of deep vein obstruction result in an overall healing rate of approximately 90% and extremely low recurrence rate of 11.4% at 1 year. However, it is critical to understand that this is in the EVRA cohort of ulcers of 3-month duration on average and of relatively small size (< 8.2 cm). There were 1,772 VLUs excluded because they were older than 6 months. It would be important to assess the outcomes in these patients with older and recalcitrant ulcers.

Almost all patients with venous ulcers undergo assessment for both venous reflux and obstruction (pelvic venous duplex and/or axial imaging). Every patient with occlusive iliocaval disease undergoes recanalization of the occluded veins first. We then wait for a few weeks, and we may also repeat the reflux test. We do not perform superficial vein ablation if the reflux has improved/corrected and if the ulcer has healed. However, if the obstruction is mild to moderate, we individualize care based on the patient's age, history of DVT, state of the infrainguinal deep vein disease, comorbidities, other causes of edema, and response to the initial superficial venous therapy.

Which scenarios lead you to treat perforators? How do you go about doing so when needed?

Mr. Gohel: We have a very conservative approach with perforators. For patients with truncal superficial venous reflux with incompetent perforators, we generally ablate superficial reflux first and assess the clinical response. If symptoms persist and perforators remain incompetent, then perforator ablation is considered. The modality for perforator ablation depends on the size and anatomy, but thermal ablation, ultrasound-guided foam sclerotherapy, and surgical ligation are all good options.

Dr. Kolluri: Although perforator treatment was quite frequently performed 5 years ago, in our practice, this is now reserved as a last intervention after axial reflux correction/periwound foam sclerotherapy and relief of proximal obstruction. When needed, we use a radiofrequency stylet combined with foam sclerotherapy for the simultaneous treatment of the perforator and the reservoir veins connected to the perforator.

Dr. Garcia: Perforators are generally treated if they are directly under a chronic ulcer, there is no deep venous disease to account for the ulcer, or a previously ablated superficial vein has recanalized with venous insufficiency into the perforator with accompanying skin changes that can be directly related to that perforator. I will first treat (ablate) the refluxing veins feeding the perforator across the level of the perforator, and if the clinical issue remains, I will directly access the perforator and treat with ultrasound-guided sclerotherapy.

What is the next frontier in either the randomized trial setting or registry-based data collection? What are the key questions going forward, and how are they best addressed?

Dr. Garcia: I believe the next key issue to address is whether deep or superficial disease should be treated first and which is more cost-effective and clinically relevant. A multicenter randomized trial will be needed to address this issue.

Dr. Kolluri: EVRA gave us several answers, but there are still several unanswered questions, as previously discussed. Postmarket registries or randomized controlled trials will certainly add to the knowledge gained from the EVRA trial. Industry partners and investigators interested in VLUs must concentrate on the outcomes of patients with long-standing VLUs that are recalcitrant, as this is a common problem.

We don't really know which is more important physiologically—obstruction, reflux, or both. We need to understand this better. Also, although IVUS has become a gold standard in the assessment of obstruction, we need physiologic assessment to accompany this anatomic assessment. Not every patient who undergoes iliac vein stenting has the expected relief of symptoms, as we all have seen. We need to have better tools to identify pathologic obstructions. Clinical appropriateness is critical. The need to curb unnecessary iliac vein stenting is as important as the need to educate primary care physicians about identifying reflux and obstruction. Interplay of the cardio-veno-lymphatic system and obstructive sleep apnea is one of our research interests as well, as not much is known. Stay tuned for the results of our study.

Mr. Gohel: We have made enormous strides in building the evidence base for superficial venous interventions with large randomized clinical trials such as the EVRA study. However, high-quality evidence in deep venous interventions remains scarce, particularly for the treatment of chronic venous outflow obstruction or postthrombotic syndrome. The enormous heterogeneity in the patient population and variability of stenting interventions may make a randomized trial difficult to design. However, a prospective observational study may be a good option for increasing the evidence base for deep venous stenting.

In recent years, there have been impressive advances and innovations in venous disease, most notably in the management of deep venous disease, pelvic venous disorders, and venous compression syndromes such as nutcracker or May-Thurner syndromes. Case selection remains an enormous challenge. Because high-quality randomized clinical trials will be difficult to design for these pathologies, greater use of registries and prospective observational study designs will allow some of these questions to be addressed. Venous enthusiasts and early adopters of novel venous interventions should be encouraged to disseminate and share their experiences so that mistakes are not repeated and the great potential of venous interventions can be translated into widespread clinical practice. ■

1. Gohel MS, Heatley F, Liu X, et al. A randomized trial of early endovenous ablation in venous ulceration. N Engl J Med. 2018;378:2105-2114.