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INSIDE

Varithena: Lessons learned, optimizing outcomes, and patient engagement

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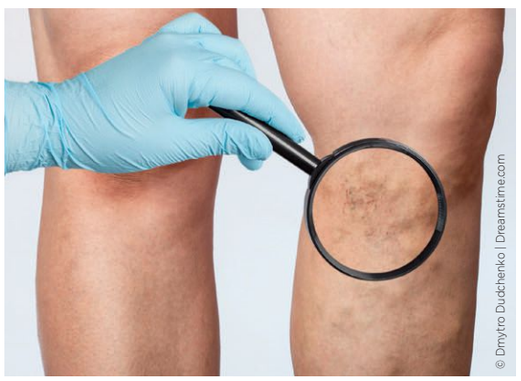
The data are staggering. An estimated 6-7 million people within the United States meet diagnostic criteria for chronic venous insufficiency (CVI)[1]. Patients classified as clinical class 2-6 (C2-C6) report that the condition interferes with their quality of life due to chronic symptoms such as pain, heavy legs, achiness, swelling, throbbing, and itching. These symptoms, often referred to as the "HASTI" symptoms, tend to worsen throughout the course of the day, affecting all aspects of patient well-being from job-related functions to sleep. With increasing numbers of patients seeking treatment for advanced venous disease and a growing arsenal of treatment options, key elements to a successful practice include optimizing treatment outcomes, including the patient in the decision-making process, and practicing evidence-based medicine with an appropriate economic return.

VARITHENA
continued on page 24



Varithena can treat a wide range of vein sizes above and below the knee, including tortuous veins and recurrent varicose veins.

New horizons in venous leg ulcer care

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INTRODUCTION

Venous leg ulcers (VLUs) are the most severe stage of chronic venous insufficiency (CVI), defined as the CEAP class C6 (open ulcers). Patients with healed ulcer belong to CEAP class C5. According to the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum, a VLU is "a full-thickness defect of skin, most frequently in the ankle region, that fails to heal spontaneously and is sustained by chronic venous disease, based on venous duplex ultrasound testing."[1]

VLUs represent 70% of all lower extremity ulcerations[2] with a prevalence between 0.06% and 2%.[1] A study within Olmsted County, MN and the Rochester Epidemiology Project (REP)[3] estimated the incidence (newly diagnosed venous ulcers) for the time frame 1991-2010 as 0.85/1000 person-year, higher than the 0.18/1000 person-year incidence reported in the same population for the period from 1966 to 1990. The incidence is much higher in individuals over 60 years of age: it was 8.9/1000 person-year in the retrospective cohort study of Olmsted County.[4] One third of the venous ulcers in the REP study[3] had a post-thrombotic etiology. The rates of post-thrombotic ulcers, according to the RIETE Registry[5], with 3-year follow-up after acute deep vein thrombosis (DVT), were 2.7% at 1 year, 4.4% after 2 years and 7.1% after 3 years. A retrospective study conducted on 3,920 primary care center electronic records in Barcelona[6] found the incidence and prevalence of VLUs doubling during a 4-year period, from 0.5 and 0.8, respectively in 2010, to 1 and 2.2 cases per 1000 person-year in 2014. More than 84% of the VLUs healed and time to healing was shorter in 2014 than before 2010 (19 weeks vs 453.9 weeks). Only 22.8% of patients were referred for vascular surgery consultation.

PATHOPHYSIOLOGY: NEW FACTS AND DISCOVERIES

The classic cascade of events leading to venous leg ulcers[7] includes venous hypertension, chronic inflammation, edema formation and skin changes, from lipodermatosclerosis to active ulcers. The initial understanding of edema formation pathophysiology was based on foundational research by Dr. Ernest Starling regarding the properties and characteristics of the absorption of fluids from connective tissue spaces.[8] In his thesis, most of the interstitial fluid resulting from arterial perfusion, re-entered the vasculature via the venule, and only 10-20% of interstitial fluid was left to the domain of the lymphatic vasculature for handling. One hundred years later the Starling concept appears to be no longer correct.[9,10] A new actor in the hemostasis of fluids was rediscovered: the endothelial glycocalyx (GCX).[11]

LEG ULCERS
continued on page 6

AVLS 35th Annual Congress 2021

The AVLS 2021 Annual Congress will be gathering at the Gaylord Rockies Resort & Convention Center in Denver, Col., from October 7 to 10. The 2021 sessions will focus on recent research in the field of venous and lymphatic disease, specifically around data from the AVLS PRO 2.0 Venous Registry. The meeting will comply with local, state and federal COVID-19 policies, including social distancing and masking. Registration limits have been increased to 700 in-person attendees. There will be up to four sessions running concurrently as well as a general session and the Innovation Pavilion. Additionally, in-person attendees will receive access to all online content, including the on-demand

AVLS
continued on page 10

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VARITHENA
continued from page 1

For years, multidisciplinary guidelines recommended that patients with mild, symptomatic disease, should manage their symptoms with compression garments worn daily. Adherence was poor and disease progression was commonplace. As disease progressed, patients could opt for surgical interventions that required invasive procedures, time away from work, and weeks to months of downtime. Many patients were reluctant to undergo invasive treatment, accepting that HASTI symptoms were an unfortunate consequence of the aging process.

ALL NEW IDEAS ARE MADE OF OLD IDEAS

Innovation is necessary in the medical field, but new approaches to venous insufficiency evolved slowly. While vascular interventions have been documented as early as the 4th century B.C.E in the writings of Hippocrates, affording centuries to evolve and refine techniques, sclerosant foam is a relative neophyte in the venous insufficiency armamentarium. Although the modern piston syringe was not invented until later, use of sclerotherapy was first documented in the 1680s.[2] Modern sclerotherapy technique advanced in the United States in the 1930s by McCausland who published data from 10,000 patients treated with his technique.[3] Since then, injection sclerotherapy became a preferred treatment for spider veins and telangiectasias. Soon after, combining sclerosant liquids with various compositions of carbon dioxide and room air created a sclerosant foam, or physician compounded foam (PCF) that was developed for use in larger veins. PCF was limited in its clinical efficacy and overall safety profile due to variable physical characteristics related to how the PCF was prepared, the liquid to gas ratio, bubble size, and the presence of room air containing high levels of nitrogen.[4,5] These physical characteristics result in highly variable, unstable, and inconsistent foam preparations. Efficacy rates were consistently sub-par when compared with thermal ablation and the presence of large bubbles and nitrogen caused rare, but serious, adverse neurological and cardiac events.[6-10] Consequently, for several decades, PCF was niched as a treatment modality solely to be used for smaller veins.

Innovation was needed, as sclerosant foam had incredible utility. It is not limited by patient anatomy (e.g. tortuous or below-knee segments) or previous procedures (e.g. patients with fibrous scar tissue or synechiae). It could be used regardless of vein size, shape, or tortuosity and it could be administered above and below the knee. It is accepted across the profession that in patients with advanced venous disease (C4-C6), skin changes made certain interventions less desirable. In these patients, foam sclerotherapy is an ideal treatment to access subdermal beds that lie beneath active and healed ulcers.

After over a decade of research, the first use of Varithena® was in August 2014 in the United States. Varithena received FDA approval for the treatment of incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein (GSV) system above and below the knee with diameters up to 25.9 mm.[11,12] Varithena microfoam composition was optimized to promote optimal endothelial destruction despite a low (1%) polidocanol concentration [13, 14]. This was accomplished by using a proprietary canister that produced cohesive, low nitrogen (<0.8%) microfoam with uniform density, bubble size, and stability to ensure optimum circumferential contact with the vascular lumen.[14, 15]

LESSONS LEARNED

For many, there was a learning curve with Varithena following FDA-approval which impeded prevalent use. Factors leading to hesitancy were reservations about DVT rates, practice economics, treatment outcomes, and appropriateness for use in axial veins. Much has progressed since FDA-approval to address hesitancy to use Varithena, including implementation of Category I CPT codes (CPT 36465, 36466), publication of real-world evidence, and applying aspects of shared decision making when discussing treatment options with patients.

Early on, the intuitive approach was to use Varithena in the same manner as PCF. This resulted in reports of DVT, superficial phlebitis, and confusion around the appropriate volume of Varithena needed to treat an incompetent GSV above the knee. This was similar to what was observed with early users in the clinical trials, with reported DVT rates that were higher than other ablative methods.[4,6,15]. With increased use of Varithena, we have gained a new appreciation for the importance of patient selection and treatment protocols that were often overlooked or dismissed as "not essential". These include following the FDA labeled Instructions for Use, carefully selecting access point (proximal to thigh perforators), elevation of the leg to 45° for the entire procedure, administration volume (not to exceed 5 mL per injection, or 15 mL per treatment session), wrapping of the elevated leg post-treatment, and patient after care (walking and wearing compression bandages as indicated by provider).

Many have incorporated and mastered these key elements of the Varithena technique. In fact, three recent studies report outcomes and closure rates in real-world settings following Varithena treatment. Closure rates were measured in these studies, adding to the evidence base that Varithena outcomes are on-par with other endovenous ablation technologies. In one study, the investigator measured patient outcomes in 250 symptomatic patients with C2-C6 disease treated with Varithena. Patients were followed for 16 ± 7 months post-treatment. Sixteen (6.4%) of the patients had skin ulcers, and 56 (22.4%) were treated previously with thermal or surgical interventions. Elimination of venous reflux and symptom improvement was documented in 94.4% of patients. Minor adverse events included asymptomatic DVT in two patients (1%) and a common femoral vein thrombus extension in one patient.[16]

A second study explored outcomes with a shortened period of compression stocking wear post-treatment. Although published guidelines recommend the use of compression stockings post-ablation,[25] it has been a topic of debate. As indicated above, part of the post-treatment Varithena protocol is for the patient to wear compression bandages for 48 hours post-treatment and compression stockings for two weeks post treatment.[4, 6,15] In this study, despite wearing compression stockings for less time (24–72 h) after the Varithena procedure,[26] the authors reported a 93% closure rate at six months post treatment, and the incidence of thrombophlebitis was similar to what is reported for other endovenous ablation techniques.[26]

A final study was undertaken to highlight the importance of each aspect of the Varithena procedure on patient outcomes. This study conducted a database review of electronic patient records from 129 limbs in 99 patients treated with Varithena. For all patients, adjunctive techniques during treatment included elevation of the leg >45°, ultrasound mapping and digital occlusion of large perforator veins, restricting the volume of Varithena used per session, and applying compression bandages to the limb while it was elevated. Closure rate was 95% with 81% overall symptomatic relief at the final follow-up, which was a mean of 113.5 days. When following protocol, DVT rates were still below those reported in the pivotal studies, with two limbs (1.75%) requiring postoperative anticoagulation for thrombus extension.[17]

In each of these investigations, the authors describe their methodology for the Varithena technique. The common denominator across studies is the strict adherence to the Varithena instructions for use during and after each procedure. This careful execution of the Varithena technique likely contributed to clinical outcomes at least equivalent to thermal ablation and improved patient-reported satisfaction in symptom resolution. Most importantly, reports of adverse events were minimal and within the range reported following other venous ablation interventions.

OPTIMIZING OUTCOMES

There has been significant emphasis on shifting the focus of treatment to the patient. Effective use of patient reported outcomes (PROs) allows the physician to focus on how the patient is feeling pre- and post-treatment, complimenting information provided by physical assessment scores. Additionally, offering patients decision aids about the pros and cons of various treatment options (e.g. pain, cost, downtime, lots of needle sticks/less needle sticks, compression/no compression, return to work and physical activity timelines) helps patients choose the best treatment for their various physical, emotional needs, and financial situation. Patients who engage with their providers in shared decision making practices are typically more satisfied, more engaged in their care, and more likely to follow the agreed-upon treatment plan, a key factor that may lead to improved outcomes.[18] Healthcare organizations are placing increased value on the benefits of patient engagement, with evidence to support that patient engagement has a positive effect on clinical quality, it reduces costs, and is good for healthcare revenue cycles.[19]

A distinction among the Varithena pivotal trials is that closure rates were not primary outcome measures. This was due to a 2009 mandate by the FDA requiring that industry use PROs as a primary outcome because this measure would best inform how a patient felt and functioned as a result of treatment.[20] To do this, the primary endpoint chosen in the Varithena clinical trials was the change in VVSymQ score. The VVSymQ instrument is a five-item tool developed in accordance with the FDA Guidance for PROs to evaluate varicose vein symptoms from the patient's perspective.[21] This instrument focuses on the HASTI

VARITHENA
continued on page 26

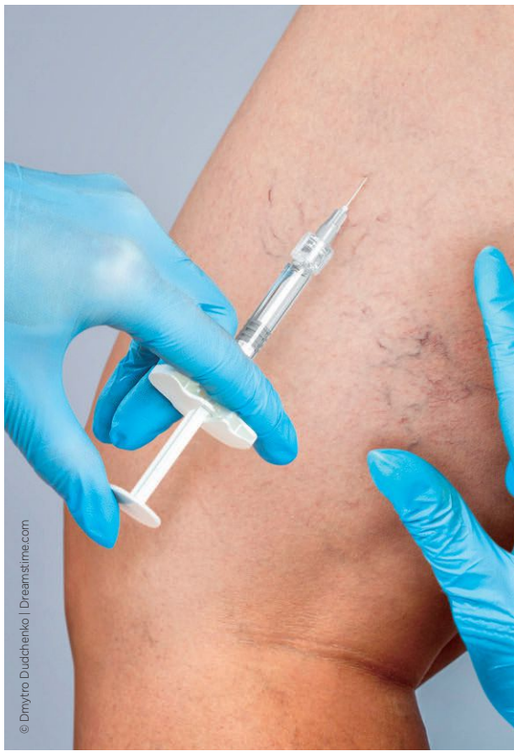
VARITHENA

continued from page 24

symptoms, those most relevant to patients with varicose veins. For example, patients with all symptoms all the time would receive a score of 25, and those with no symptoms any of the time would receive a 0. Reductions in VVSymQ score equate to HASTI symptom improvement.

In one randomized, placebo-controlled, multicenter study, HASTI scores were documented at baseline and eight weeks post-treatment. The authors documented that Varithena provided significantly greater symptom relief compared with placebo and the HASTI score correlated highly with the modified-VEINES-QoL/Sym and Chronic Venous Insufficiency Questionnaire-2 scores ($r = 0.7$ to > 0.9, $p \leq 0.001$).[22] A subsequent trial reported that 8-weeks post-treatment, VVSymQ scores for patients treated with Varithena were significantly superior to placebo in terms of symptom resolution. It is important to document that in this patient population, vein diameters ranged from 1.5–25.9 mm, and vein diameter had no impact on the magnitude of improvement in PROs, with patients demonstrating uniform improvement regardless of vein size[12]. In the final pivotal study, results from previous studies were repeated in a new set of patients, with patients in the Varithena group having a greater improvement in symptoms than placebo-treated patients.[11] A final study documented the durability of symptom resolution one-year post-treatment. In that study, patients treated with Varithena demonstrated consistent, durable, and clinically meaningful improvements in symptoms, as measured by reductions in mean VVSymQ score. These data, and adherence to the FDA mandate, allowed Varithena to include symptom resolution on labeling claims.[20] This is of critical importance when engaging patients in shared decision-making conversations around treatment options. Indicated improvement in symptoms may resonate strongly with patients.

Lessons learned over the past several years have moved microfoam chemical ablation/Varithena out of its niche. With an excellent safety profile and clinical- and real-world outcomes data similar to those of other catheter-based modalities, Varithena can be used to treat a wide range of vein sizes above and below the knee, including tortuous veins and recurrent varicose veins. Varithena maintains a robust dataset to support its impact on patient reported outcomes and symptom improvement. As a minimally invasive procedure, with one or two needle sticks required per treatment, many patients may opt for Varithena during shared decision making around treatment options. Appreciation for how Varithena behaves in the lumen due to its optimized physical properties, and adherence to the FDA labeled Instructions for Use protocol, enables us to treat the GSV and its tributaries at the same session in selected patients. In sum, the transition from niched use of PCF to widespread use of Varithena has taken time. Despite this, the result is a growing body of evidence detailing Varithena's safety and efficacy profile on par with other ablative modalities, an appreciation for the need to adhere to the instructions for use during treatments, and a new opportunity to discuss treatment options with patients from a perspective of symptom resolution, and clinical outcomes. In the coming years, additional real-world data will contribute to the rich evidence base. Ideally, publication of a meta-analysis will facilitate decisions about the utility of Varithena across the venous disease landscape. **VTN**



REFERENCES

1. DePopas E, Brown M. Varicose Veins and Lower Extremity Venous Insufficiency. *Semin Intervent Radiol*. Mar 2018;35(1):56-61. doi:10.1055/s-0038-1636522
2. Goldman MP, Bergan JJ. *Sclerotherapy : treatment of varicose and telangiectatic leg veins*. 3rd ed. Mosby; 2001:xxii, 401 p.
3. McAusland S. The modern treatment of varicose veins. *Med Press Circular*. 1939 1939;201:404-410.
4. Asbjornsen CB, Rogers CD, Russell BL. Middle cerebral air embolism after foam sclerotherapy. *Phlebology*. Dec 2012;27(8):430-3. doi:10.1258/phleb.2011.011002
5. Malvehy MA, Asbjornsen C. Transient neurologic event following administration of foam sclerotherapy. *Phlebology*. Feb 2017;32(1):66-68. doi:10.1177/0268355516628721
6. Brittenden J, Cooper D, Dimitrova M, et al. Five-Year Outcomes of a Randomized Trial of Treatments for Varicose Veins. *N Engl J Med*. Sep 5 2019;381(10):912-922. doi:10.1056/NEJMoa1805186
7. Brittenden J, Cotton SC, Elders A, et al. A randomized trial comparing treatments for varicose veins. *N Engl J Med*. Sep 25 2014;371(13):1218-27. doi:10.1056/NEJMoa1400781
8. Siribumrungwong B, Wilasrusmee C, Orrapin S, et al. Interventions for great saphenous vein reflux: network meta-analysis of randomized clinical trials. *Br J Surg*. Apr 5 2021;108(3):244-255. doi:10.1093/bjs/znaa101
9. Yiannakopoulou E. Safety Concerns for Sclerotherapy of Telangiectases, Reticular and Varicose Veins. *Pharmacology*. 2016;98(1-2):62-9. doi:10.1159/000445436
10. Bush RG, Derrick M, Manjoney D. Major neurological events following foam sclerotherapy. *Phlebology*. 2008;23(4):189-92. doi:10.1258/phleb.2007.007073
11. Todd KL, 3rd, Wright DI, Group V-I. The VANISH-2 study: a randomized, blinded, multicenter study to evaluate the efficacy and safety of polidocanol endovenous microfoam 0.5% and 1.0% compared with placebo for the treatment of saphenofemoral junction incompetence. *Phlebology*. Oct 2014;29(9):608-18. doi:10.1177/0268355513497709
12. King JT, O'Byrne M, Vasquez M, Wright D, Group V-I. Treatment of Truncal Incompetence and Varicose Veins with a Single Administration of a New Polidocanol Endovenous Microfoam Preparation Improves Symptoms and Appearance. *Eur J Vasc Endovasc Surg*. Dec 2015;50(6):784-93. doi:10.1016/j.ejvs.2015.06.111
13. Carugo D, Ankrett DN, O'Byrne V, et al. The role of clinically-relevant parameters on the cohesiveness of sclerosing foams in a biomimetic vein model. *J Mater Sci Mater Med*. Nov 2015;26(11):258. doi:10.1007/s10856-015-5587-z
14. Carugo D, Ankrett DN, Zhao X, et al. Benefits of polidocanol endovenous microfoam (Varithena(R)) compared with physician-compounded foams. *Phlebology*. May 2016;31(4):283-295. doi:10.1177/0268355515589063
15. Eckmann DM. Polidocanol for endovenous microfoam sclerosant therapy. *Expert Opin Investig Drugs*. Dec 2009;18(12):1919-27. doi:10.1517/13543780903376163
16. Deak ST. Retrograde Administration of Ultrasound-guided Endovenous Microfoam Chemical Ablation (UMCA, Varithena) for the Treatment of Superficial Venous Insufficiency. *Journal of Vascular Surgery*. 2018;
17. Jimenez JC, Lawrence PF, Woo K, et al. Adjunctive techniques to minimize thrombotic complications following microfoam sclerotherapy of saphenous trunks and tributaries. *J Vasc Surg Venous Lymphat Disord*. Jul 2021;9(4):904-909. doi:10.1016/j.jvsv.2020.11.015
18. Elwyn G, Cochran N, Pignone M. Shared Decision Making – The Importance of Diagnosing Preferences. *JAMA Internal Medicine*. 2017;177(9):1239-1240. doi:10.1001/jamainternmed.2017.1923
19. Gittlen S. Health Care Providers on the Problems of Patient Engagement Design. *NEJM Catalyst*. 2017;3(5)
20. Administration USDoHaHSFaD. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009; www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
21. Paty J, Turner-Bowker DM, Elash CA, Wright D. The VVSymQ(R) instrument: Use of a new patient-reported outcome measure for assessment of varicose vein symptoms. *Phlebology*. Aug 2016;31(7):481-8. doi:10.1177/0268355515595193
22. Gibson K, Kabnick L, Varithena 013 Investigator G. A multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena(R) (polidocanol endovenous microfoam 1%) for symptomatic, visible varicose veins with saphenofemoral junction incompetence. *Phlebology*. Apr 2017;32(3):185-193. doi:10.1177/0268355516635386