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Novel Approaches to Arteriovenous Access Creation, Maturation, Suitability, and Durability for Dialysis

M. V. DeVita
Zucker School of Medicine at Hofstra/Northwell, mdevita@northwell.edu

S. K. Khine
Northwell Health, skhine1@northwell.edu

H. Shivarov

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Maria V. DeVita[1], San Kyaw Khine[1] and Hristo Shivarov[1]

[1]Division of Nephrology, Lenox Hill Hospital, Northwell Health, Zucker School of Medicine, New York, New York, USA

Since the arteriovenous fistula (AVF) was first conceived over 50 years ago, the goal to create a vascular conduit with predictable and reproducible maturation and durability continues to elude caregivers. Recently, however, advances in the understanding of vascular biology and new technologies now provides us with some optimism; we are moving toward a viable solution. A quickly maturing, sustainable, and durable arteriovenous access may soon be attainable. This review will discuss these advances. There are novel approaches to AVF creation and devices to enhance maturation, advances in arteriovenous graft material(s), and devices to safely prolong the use of tunneled dialysis catheters. Although hemodialysis (HD) access remains a complex problem, these innovations may lead the way to optimizing the care and the quality of life of those patients who have no choice but to proceed with HD.

The creation and maturation of the ideal AVF remains elusive. The goal to simply create a conduit for vascular access for HD, with predictable and reproducible maturation, and with durability continues to be difficult to obtain despite many attempts to address this problem. The reasons for this elusiveness are myriad. First, we, as clinicians, still cannot precisely determine who will progress to end-stage renal disease (ESRD) or, if there is progression, when dialysis will need to be initiated (e.g., onset of uremic symptoms). As a result, we lack evidence and guidance as to when optimally to create an AVF. The Fistula First, Catheter Last Initiative[1] recommends creation of an AVF at least 6 months before the anticipated start of HD. However, the gap between unnecessary creation of AVF and initiation of HD with a catheter is large. O'Hare *et al.*[2] reported that there are multiple trajectories of progression, so that as many as 10% to 17% of patients will not ever have their AV access used because they have not reached ESRD. At the other end of the spectrum, approximately 80% of patients on new-start HD still initiate HD with a catheter. Based on the United States Renal Data System (USRDS) 2018 Annual Report, at the time of initiation of HD, 62.5% of patients start treatments with a catheter only. Those with catheters and maturing fistula or grafts (AVG) are 16.1 % and 1.6 %, respectively. Sole AV fistula and graft use is a mere 16.7 % and 3.0 %, respectively. In many patients on HD, the AV fistula remains the most common vascular access (64.5%), followed by patients with catheters (18.9 %) or AVG (16.6 %).[3] Furthermore, the Dialysis Access Consortium (DAC) trial showed that as many as 60% of AVFs were not suitable for dialysis at 6 months and that these nonmaturing AVFs need up to 3 supplemental procedures to achieve suitability for dialysis.[4] The dysfunction is usually as a result of initial failure to mature or, after maturation, the development of venous stenosis (and/or thrombosis). Indeed, many AVFs created require interventions to facilitate maturation.[5]

This problem is in contrast to the relative ease of initiation of peritoneal dialysis (PD). For PD, when a patient becomes mildly uremic, PD catheter placement is scheduled. The surgical site generally heals within a few weeks, and PD training can start unencumbered. Dialysis starts predictably and with durability of access (although not every catheter works perfectly). Likewise, an AVG can be placed and used within a

predictable time frame. However, AVGs are not durable; they have very high rates of stenosis, thrombosis, and infection. Finally, a tunneled HD catheter is also predictable but not safe or durable over time.

In addition to being unable to determine the timing of initiation of dialysis precisely, we have a poor understanding of the vascular biology and changes to the vasculature that transpire once an AV access is created. To improve outcomes, we need to develop therapies or techniques to secure the primary maturation of AVF or avoid stenosis, thrombosis, and infection in AVG and avoid infections and clots in catheters.[6] To this end, recent focus has been on the vascular biology of arteriovenous accesses. By evaluating vasopathic or vasoprotective molecules, novel approaches are being explored. These approaches address the problem of inward remodeling: a reduction of luminal diameter due to neointimal hyperplasia or address insufficient outward remodeling, increasing luminal diameter by vasodilation, and/or structural enlargement. This latter process mitigates against inward remodeling by maintaining adequate luminal diameter in the face of neointimal hyperplasia.[7,8]

At present, most of our attention is placed on addressing maturation failure weeks to months after the creation of the AVF. The newer novel approaches are applied at the time of the creation of the AVF. To better understand these approaches, it is important to have some knowledge of the cellular and molecular aspects of arteriovenous access dysfunction.

Typically, failure of an AVF to mature is a characteristic juxta-anastomotic stenosis from either venous constriction or venous neointimal hyperplasia (NIH).[7] Briefly, this latter pathology is thought to be the result of endothelial and smooth-muscle injury from shear stress, turbulent flow, and/or tissue injury at time of surgery. This injury then triggers activation of myofibroblasts and fibroblasts within the endothelial wall, also generating expression of cytokines and other mediators, such products as endothelin, platelet-derived growth factor (PDGF), vascular endothelial growth factor, and transforming growth factor beta (TGF-β). Subsequently, venous neointimal hyperplasia results from the migration of smooth muscle cells and myofibroblasts from the media to the intima. In addition, there is ongoing proliferation, inflammation, and oxidative stress. Furthermore, there may also be adventitial angiogenesis and proliferation of macrophages that line the perivascular region.[6] NIH has long been thought to be the culpable process in failure of AVF maturation. However, recent studies call this singular event into question.[9,10] What is known is that an imbalance between NIH, inward remodeling (too much), and vasodilation, outward remodeling

(inadequate), leads to access failure. The mechanisms within the milieu of the perivascular anastomotic region still need to be fully elucidated.

Another demonstrated feature in failure of AVF is related to poor artery or vein selection (too small, too deep). As the science of AV access creation has evolved, it is now clearly recognized that the vessels used to create an access have to be of proper size and quality. Standard vessel criteria for creation of access that have now been generally accepted are a vein diameter for AVF of 0.25 cm and for an AVG 0.4 cm with an artery diameter of 0.2 cm.[11] The vessels must also be superficial enough to enable easy palpation and cannulation. Presurgical vessel mapping is now mandatory.

A recent concern is that the surgical procedure itself can cause vascular injury, thereby contributing to failure of AVF maturation. This is thought to be the result of stretching and manipulation of the vein when handled during surgery. In addition to cellular factors, there is hemodynamic stress at anastomotic sites, producing turbulent flow.[12] Finally, an important factor contributing to access stenosis is endothelial and smooth-muscle cell injury from angioplasty.[13]

The first description of an AVF for chronic intermitted HD was the Brescia-Cimino radiocephalic fistula, reported in 1966.[14] This simple procedure of connecting one's own artery to a draining vein, thereby internalizing the AV access, was revolutionary. Typical anatomic sites used today are the radiocephalic, brachiocephalic, and basilic vein transposition. Previous conduits had external components that were susceptible to infections and thromboses and were not durable. Unfortunately, over the past 50 years there have not been any major breakthroughs to resolve the problems associated with AV access: failure to mature, infection, stenosis, and thrombosis. This problem remains a tremendous gap toward optimizing the care and quality of life for those patients on HD.

For a prosthetic AV graft, venous stenosis develops. The subsequent reduced flow facilitates formation of a thrombosis at the graft-vein anastomosis or in the proximal vein. An artery-graft stenosis may also occur and precipitate thrombosis. Venous stenosis in the AVG is usually the result of neointimal hyperplasia[7] (in contrast to AVF, in which this is less clear).

This review will discuss novel therapies to improve creation of AV access, maturation, and suitability for dialysis. First, there are new devices to create AVF from an endovascular approach. Then, of interest, are 2 devices to help optimize the configuration of the vascular anastomosis. There are several explorations into therapies being tested that aim to enhance primary maturation by addressing changes to the vasculature at the time of AVF creation. Another area

Table 1. Endovascular devices

Device	Design	Entry	Anastomotic technique	Notes
Ellipsys Vascular Access System (Avenu Medical, San Juan Capistrano, CA)	Single-catheter venous access system Ultrasound-guided	Retrograde venous access obtained Contact between deep communicating vein and proximal radial artery	Jaws of device puncture vein and artery walls, side to side Tissue fusion to cut and weld an elliptical anastomosis between the artery and vein Tissue fusion requires heat and pressure to be applied at the same time	Usually requires another procedure to promote arterial flow through the anastomosis or to outflow traits
everlinQ endoAVF system (TVA Medical, Becton Dickenson and Company, Franklin Lakes, NJ)	Two catheters, 1 arterial, 1 venous; magnets establish alignment between closely approximated deep vessels in forearm Ultrasound and angiographic guidance	Brachial vein and artery approach–contrast use guide movement to ulnar artery and vein	Side-to-side by radiofrequency energy generated from venous catheter and ceramic backstop in arterial catheter. Slit by tissue vaporization	Usually requires embolization of brachial vein (used for access) to help augment flow into superficial veins

includes those therapies that address failure of maturation and development of stenoses and/or thromboses. In addition, there will be a discussion on various modifications to AVGs. Finally, there are 3 new devices/therapies to limit infection and clotting of central venous catheters (CVCs).

Devices for Creation of AVF

There are 2 new FDA approved devices to create an AVF via an endovascular approach: the everlinQ endoAVF system (TVA Medical, Becton Dickenson and Company, Franklin Lakes, NJ) and the Ellipsys Vascular System (Avenu Medical, San Juan Capistrano, CA) (Table 1).

The everlinQ endoAVF system employs 2 catheters, each with a series of magnets. The creation of the AVF consists of cannulation of both the brachial vein and the brachial artery. These magnetic catheters are then advanced into the ulnar vein and artery, respectively. The magnets embedded within the catheters are attracted and align. Once in position, a radiofrequency pulse generated from an electrode is deployed and creates the anastomosis between these ulnar vessels. The device was evaluated in the Novel Endovascular Access Trial (NEAT).[15] A single-arm, multicenter study, it evaluated the safety and efficacy of creating AVF using this percutaneous/endovascular system. The efficacy end points of the study were.

AVF physiologically suitable for dialysis, defined as brachial artery flow > 500 ml/min, vein diameter > 4 mm, and functional usability of the endoAVF. Fifty-nine patients were included in the final analysis. Of these, 87% of the patients had a physiologically suitable AVF; however, functional usability as determined by dialysis nurses was 64%. In addition, only 52% were functional without any interventions; the remainder needed secondary interventions to assist maturation. There are now 6F and 4F introducers for cannulation of the brachial artery and vein, and radial or ulnar systems, respectively. Of note, coiling of the

brachial vein seems critical to the success of creation of the AVF and has its own set of consequences.

The Ellipsys Vascular Access System (Avenu Medical, Inc., San Juan Capistrano, CA) involves a thermal resistance anastomosis device (TRAD).[16] Here, a single catheter is used to create a percutaneous fistula under ultrasound guidance. After cannulation of a deep communicating vein, the catheter is advanced in a retrograde fashion. A closely aligned portion of the proximal radial artery is selected for access. The jaws of the device puncture through the closely approximated walls of both vessels. The catheter then generates thermal energy to fuse the artery and vein, creating an elliptical anastomosis.

The efficacy and safety of TRAD was also recently evaluated.[16] Twenty-six patients underwent creation of AVF, with a success rate of 88% (23 of 26 patients). At 6 weeks, 87 % of the AVF were patent, and 80% were used for HD at 3 months. However, the need for additional procedures—such as balloon dilation, vein embolization, vein ligation, venous transposition, and valvulotomy—were common, being required in 87% of AVFs. No major complications related to the device were documented.

Neither of these 2 products has been tested against more traditional means of AVF creation. It is also important to note that these percutaneously created fistulae are low flow, and successful use will need to be accompanied with education about the AVF and proper cannulation. A recent review describes these 2 techniques in greater detail.[17]

Two devices that aim to enhance the success of traditional surgical AVF creation and maturation are being tested. These devices seek to optimize the geometrical configuration of the fistula, thereby minimizing turbulence, promoting laminar flow, and attenuating NIH.

The VasQ (Laminate Medical Technologies, Tel Aviv, Israel) is an external conduit support system for vascular access, which is placed at the time of creation

Figure 1. VasQ device (Laminate Medical Technologies, Tel Aviv, Israel). Reprinted with permission from *Vascularnews*. Laminate receives IDE approval from FDA to initiate study of the VasQ device. Available at: https://vascularnews.com/laminate-receives-ide-approval-fda-initiate-study-vasq-device/. Accessed January 6, 2020.[18]

of AVF (Figure 1).[18] The device externally surrounds and supports the index vein and artery near and around the anastomosis, acting as a scaffolding to preserve the ideal angle of anastomosis. It is purported to reduce turbulent flow and prevent neointimal hyperplasia.[19]

A small clinical trial with 20 patients was performed to test the product. All the patients were implanted with VasQ at the time of creation of AVF. The end points were venous flow, primary patency, and unassisted maturation rates of the AVF. The patency rates were 95%, 79%, and 79% at 1, 3, and 6 months, respectively; maturation rates were 80%, 79%, and 74%, respectively. At the 6-month follow-up, 14 of 15 patients who required HD were able to have their AVFs cannulated. A larger study examining the efficacy of VasQ is actively recruiting a target of 80 patients (NCT03246984) undergoing creation of a new brachiocephalic (50 patients) or radiocephalic (30 patients) AVF. The follow-up period to assess the patency and freedom from any intervention to maintain or reestablish patency will be 12 months and is expected to be completed in mid-2020.[20]

In contrast to the external VasQ device, the Optiflow device (Bioconnect Systems, Fort Washington, PA) is an implantable anastomotic connector, also used to standardize the creation of AVF at a set angle (Figure 2).[21] This nonthrombogenic silicone-polyurethane connector is inserted during the surgery to sit within the anastomosis of the AVF to maintain a set luminal size to optimize flow. The placement and configuration allow for consistency in both the size and the angle of the arterial anastomosis. The concept is that, by using this device, the geometry and flow path at the anastomosis is predetermined and predictable, thereby attenuating the likelihood of inflow stenosis, turbulent flow, and perhaps NIH. The OPEN (Optiflow PatEncy and MaturatioN) study, published in 2014, showed promising results in 41 subjects undergoing creation of a new AVF, permitting progression to a phase 3 trial.[22,23] There are no new data on this product available at this time.

Devices/Therapies to Enhance AVF Maturation

There have been multiple trials investigating products to reduce neointimal hyperplasia, enhance dilation of blood vessels used for AVF, or interfere with the blood clotting processes, including—but not limited to—use of clodipogrel, statins, fish oil, aspirin, and coumadin. Most have been unsuccessful.[4,24,25]

New products all seek to enhance maturation rates by applying or adding the product at the time of creation of AVF and aim to reduce tissue inflammation and NIH. These can be considered *a priori* interventions. In contrast, the standard approach today is postcreation, maturation-failure interventions: procedures employed at a time after AVF creation/use (Table 2).[26]

As described previously, creation of the AVF is associated with hemodynamic changes and vascular injury that can cause cells in the middle and outer vessel wall layers to secrete extracellular material and proliferate. These events can result in intimal hyperplasia, stenosis, and thrombosis of the AVF. The novel therapies all address this vascular biology, some with limited success.

Sirolimus

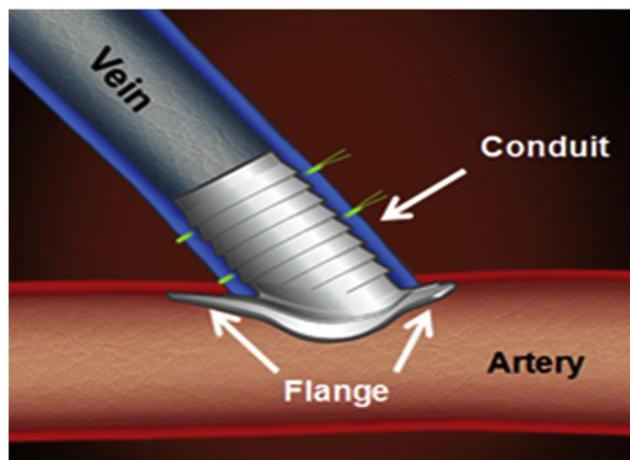The sirolimus-eluting collagen membrane (SeCM) is an investigational product developed for the

Figure 2. Optiflow implant (Bioconnect Systems, Fort Washington, PA). Reprinted with permission from Yevzlin AS, Valliant AM. Interventional nephrology: novel devices that will one day change our practice. *Clin J Am Soc Nephrol.* 2013;8:1244–1251.[21] Copyright © 2013 by the American Society of Nephrology.

Table 2. Local drug delivery products at time of AVF creation

Product	Status	Trial name(s)	Sponsor
Sirolimus	Completed recruitment July 2019, ongoing 6- and 12-mo data	Trial to Evaluate the Sirolimus-Eluting Collagen Implant on AV Fistula Outcomes (ACCESS), NCT 02513303	Vascular Therapies
Human Acellular Vessel (HAV, Humacyte, Inc, Durham, NC)	Ongoing phase-3 trial	NCT 03181245	Humacyte
Vonapanitase	Completed phase-3 randomized controlled trial, spring 2019	PATENCY-1 PATENCY-2 NCT 01305824 NCT 02110901	Proteon
Vascugel	To date no phase-3 trial	NCT01806545	Shire
Paclitaxel-eluting Mesh	Terminated 2011 for imbalance in graft infection between groups	NCT 00448708	Angiotech

AVF, arteriovenous fistula.

intraoperative local perivascular delivery of sirolimus. The product, a sirolimus-impregnated collagen wrap, is applied circumferentially at and around the site of the vascular anastomosis, just after successful creation of the AVF. Sirolimus has clinically proven anti-proliferative properties when used in coronary artery percutaneous coronary intervention.[27] Initial data using the product in AVG were promising.[28] The utility in enhancing maturation of AVF is now under investigation in a randomized, multicenter single-blind controlled study evaluating arteriovenous outcomes with and without perivascular simolimus-eluting collagen implant (SeCl) in subjects on HD (Trial to Evaluate the Sirolimus-Eluting Collagen Implant on AV Fistula Outcomes [ACCESS]), NCT 0251330). Patient recruitment was completed in July 2019. Six- and 12-month data are expected in the beginning of 2020.

Vonapanitase

Vonapanitase (PRT-201) is a recombinant human chymotrypsin-like elastase that can cleave peptide bonds in the protein elastin found in vessel walls. Applying vonapanitase during AVF surgery, immediately following successful creation of the AVF, is thought to augment maturation of the fistula patency and prevent formation of critical stenosis and thrombosis. The enzyme is rapidly absorbed into the outermost layer of the vessel wall, acting to enhance outward remodeling by fragmenting elastin fibers. This hypothesis was tested in PATENCY 1 (NCT02110901) a double-blind placebo-controlled study. The primary end point was primary patency, defined as the time from creation of the fistula until thrombosis or a procedure to restore or maintain the patency. The secondary end point was secondary patency, the time from creation of the fistula until abandonment. In the study, 349 patients who were on HD, or approaching it, were enrolled. Immediately after successful surgical creation of an AVF, the study-drug solution was applied topically to the artery and vein at the anastomosis for 10 minutes. The data showed no significant

improvement of primary patency but did show an increased rate of secondary patency.[29]

A follow-up trial, PATENCY-2, was a multicenter randomized, double-blind placebo-controlled trial that enrolled 603 patients with chronic kidney disease (CKD). It followed a similar protocol as PATENCY-1; the active drug solution was applied at time of radio-cephalic AVF creation. In April 2019, the sponsor company, Proteon Therapeutics (Waltham, MA), reported that the study did not achieve significance; at 12 months, 69.7% of vonapanitase-treated AVF were in use, compared with 65.1% in the control group ($P = 0.328$). Secondary patency demonstrated by Kaplan-Meier curves was also not significant between groups (78% vs. 76% respectively, $P = 0.932$). The next step in investigating the use of this product for enhancing AVF maturation has not yet been determined.

Vascugel

Vascugel (NCT 01806545) (Pervasis Therapeutics, Inc., Cambridge, MA) is a unique allogeneic endothelial cell product that uses adult-differentiated allogeneic endothelial cells (donor endothelial cells with a highly targeted biologic function) embedded in a patented polymer matrix. When applied adjacent to a blood vessel, the endothelial cells in Vascugel provide growth regulatory compounds to that underlying blood vessel, which promotes healing and may prevent excessive inflammation, thereby reducing thrombosis and stenosis. The product is placed on the outer walls of both the venous and arterial anastomoses following creation of an AVF. The formulation in Vascugel secretes factors that combat inflammation and promotes proper vascular healing, thereby reducing thrombosis (or clotting) and the formation of intimal hyperplasia. After approximately 4 to 8 weeks, Vascugel is safely resorbed by the body. In 2006, a phase 1 trial, including 8 subjects, was promising. The subsequent phase 2 trial was performed in 2007 and included 57 patients (30 AVG, 27 AVF).[30] Results showed there was no difference in early complication rates between the

Vascugel and placebo groups at 4 weeks. There was a greater than 30% increase in panel reactive antibodies in 9 of the 46 (19.5%) Vascugel-treated patients and 1 of the 19 (5.2%) placebo patients ($P = 0.26$), but there were not associated local or systemic complications. This product appears to be a safe and may enhance AV access maturation and suitability for dialysis. The company did receive the approval to move forward with a phase 3 trial in 2011, but no such study has been initiated.

There are data suggesting that patients with CKD and ESRD have endothelial dysfunction. Phosphodiesterase type 5 inhibition, which enhances the effects of nitric oxide,[31] has been hypothesized to improve endothelial function through production of nitric oxide and may help AVF maturation. A pilot study compared flow mediated dilation and venous occlusion plethysmography as well as blood flow of the AVF among subjects who ingested sildenafil or placebo before and following creation of AVF. This clinicaltrial.gov site was last updated in August 2019 (NCT02414204). It is unclear whether additional studies are being considered.

Far Infrared

Far infared (FIR) therapy to assist AVF maturation has been studied, mostly in Taiwan. These invisible electromagnetic waves are thought to improve cutaneous blood flow and thereby improve endothelial function. A wavelength between 5 and 25 mcm is applied from a far infrared wave emitted in position approximately 20 cm above the AVF anastomosis. The FIR is applied for 40 minutes during each HD treatment.[32,33] The effects are thought to be both thermal and nonthermal. NCT 04011072 is not yet recruiting subjects.

Paclitaxel

Paclitaxel was a promising agent to attenuate perivascular inflammation and promote early use of AV accesses. NCT 01033357, testing a paclitaxel-eluting mesh applied at the time of AVG placement was terminated early because of an imbalance in the number of graft infections between the treatment and control arms.[34]

Arteriovenous Grafts

Polytetrafluoroethylene (PTFE) has been the standard prosthetic material used for placement of an AVG without much change since its initial use in 1976. The product was modified to an "expanded" graft (ePTFE) years ago. The newest advancement to ePTFE includes variations to facilitate immediate or early use, referred to as "early cannulation grafts." These products all have a multilaminated structure, usually a 3 layers, with self-sealing membrane that effectively reduces suture-line bleeding and close-off puncture sites, allowing rapid cannulation—within hours to days of placement—thus obviating the need for catheters. Several products are now ready for use either in Europe, the United States, or both.[35–37] Flixene (Getinge, Wayne, NJ), Acuseal (GORE, Newark, DE), and Rapidax (Vascutek, Inchinnan, UK) are trilaminate grafts with propriety self-sealing capabilities. AVflo (Nicast, Lod, Israel) is made of polycarbonateurethane, using an electrospinning technology also enabling a rapid seal of puncture sites. These modifications are purported to limit perigraft hematomas and seromas, limit infection, and reduce formation of pseudoaneurysms. All have been tested in smaller studies affording FDA and/or European approval, but, to date, there are no randomized controlled trials of these products. Another modified AVG product, Vectra (Thoratec Corporation, Pleasanton, CA), made of polyurethane, is no longer being marketed as an early cannulation product.[38]

One prospective, nonrandomized, multicenter US clinical trial, including 138 subjects, revealed that the 6-month cumulative patency of the Acuseal Vascular Graft is comparable with that of other arteriovenous grafts, with 84% patency compared with 75% patency in the historical control. In addition, within 28 days of implantation, 75.6% of the implanted Acuseal grafts had been successfully cannulated 3 consecutive times, allowing the central venous catheter to be removed.[39] In a retrospective cohort published in 2017, consecutive patients who underwent placement of HD grafts between November 2014, and April 2016, were retrospectively identified at 2 tertiary centers. There were 148 standard (S) AVGs and 62 immediate access (IA) AVGs identified. The results suggest that IAAVGs allow earlier cannulation and tunneled catheter removal, thereby significantly decreasing catheter-related complications. Patency and infection rates were similar between the SAVG and IAAVG groups; however, fewer secondary procedures were performed in IAAVGs.[40]

Yet another "early cannulation" product with a unique proprietary design is the InnVasc (InnAVasc Medical, Durham, NC) AVG. A clinical trial is in the midst of actively recruiting subjects (NCT03645681). Primary completion is expected by the end of 2019, with study completion expected in late 2021.

Healionics (Seattle, WA) is the first company to test a new material that is not PTFE based. Their proprietary Sphere Templated Angiogenic Regeneration (STAR) biomaterial is a 3D scaffold medical-grade silicone product that has specific pore structures that allow for macrophage infiltration, which will resist infection and prevent scarring. Using this biomaterial, Healionics has

developed a synthetic AVG for HD, the STARgraft, which has demonstrated superior patency and resistance to occlusion in several animal studies. The First in Human Evaluation of STARgraft AV for Hemodialysis Access in Comparison to ePTFE Vascular Grafts study is expected to be completed by mid-2020 (NCT03916731).

Finally, the Human Acellular Vessel (HAV, Humacyte, Inc, Durham, NC) is a tissue-bioengineered conduit that uses human vascular smooth-muscle cells that are cultured onto a biodegradable polymer. These AVGs showed promise in 2 phase 2 trials (NCT 01744418 and NCT01840956).[41]

Humacyte is currently supporting 2 phase 3 trials across 40 sites in the United States, Europe, and Israel. The studies are evaluating the efficacy and safety of the blood vessel as a conduit for HD in patients with ESRD requiring renal replacement therapy.[42] Subjects are being randomized to receive either an HAV or a standard autologous AVF and will be followed for 24 months. Further follow-up for those with a patent autologous AVF and all HAV subjects will be followed for up to 60 months, with an estimated study completion date of 2023.

For those patients who have no venous anastomotic site for AVG placement or have central venous stenoses, a hybrid endovascular device, called Hemodialysis Reliable Outflow (HeRO) graft access has been available since 2008 (Merit Medical Systems, Inc., Malvern, PA). It is composed of 2 parts: a standard PTFE graft and venous outflow component, similar to a catheter. It is useful to salvage an upper extremity access site that would be otherwise abandoned. The device bypasses the stenosis or—if wire access can be obtained through a complete central vein occlusion—tunnels through the area of concern. The graft is anastomosed to the brachial artery and tunneled subcutaneously. The venous outflow component is placed percutaneously into the right atrium through the subclavian or internal jugular vein and superior vena cava, to bypass any central stenosis. These 2 components are subsequently attached to each other subcutaneously, through a specially designed titanium connector. The advantage, compared with a tunneled catheter, is that the system is completely internalized, reducing the risk of infection.[43]

A multicenter trial including 164 consecutive HeRO graft implants for HD treatment found the HeRO device performed comparably with standard AVGs and was superior to tunneled dialysis catheters (TDC) in outcomes of patency, intervention, and infection rates when compared with the peer-reviewed literature.[44]

Secondary Patency

Once it is clear that an AV access will not be suitable for dialysis, an intervention is needed. Surgical or endovascular approaches can be employed. Percutaneous transluminal angioplasty (PTA) for stenosis of AVFs was, for the first time, reported in 1981,[45] and has become the treatment of choice to address failing AVFs and AVGs. However, it is still not clear which patients will benefit most from which type of intervention, as described by Tordoir *et al.*, in a review of the topic, and may fall to the particular expertise at hand.[46]

More recently, researchers have been investigating the use of drug-eluting balloons—mainly paclitaxel—to inhibit restenosis. These drug-eluting balloons appear to decrease trauma to the endothelium, attenuating subsequent restenosis. A trial by Trerotola *et al.*[47] enrolled 285 patients with dysfunctional aAVFs at 23 centers. All patients received angioplasty of the lesion responsible for access dysfunction. Lesions were treated with either a paclitaxel-coated balloon or an uncoated control balloon. Primary patency did not differ between groups at 6 months; however, interventions to maintain target lesion patency were fewer for the drug-coated balloon at 6 months (0.31 vs. 0.44 per patient; $P = 0.03$).

In another study by Haave *et al.*,[48] standard PTA was compared with paclitaxel drug-coated balloons (DCBs) to investigate the patency after treatment of restenosis in radiocephalic AVFs. Twenty-six patients (13 PTAs and 13 DCBs), who received at least 1 previous PTA and required a repeat intervention at the same anatomic location, were included. After 12 and 24 months, the estimated proportions of stenosis-free patients were 61% and 31%, respectively, in the DCB cohort, compared with 40% and 15%, respectively, in the PTA cohort. Patients treated with DCB had significantly longer patency than patients in the PTA cohort (median 16 vs. 5 months, $P = 0.05$). These data were confirmed in a longitudinal follow-up of 147 patients.[49] There has been concern about morbidity and mortality with DCB; however, a recent meta-analysis, ILLUMENATE, found mortality rates for patients treated with DCB and uncoated PTA were indistinguishable over 3-year follow up.[50] Certainly, additional studies are needed. At present, owing to the expense, DCBs are usually reserved for resistant stenoses and appear to extend the need for reintervention by a few months.

Central Venous Catheter

Although dialysis catheters are not desirable access, they are here to stay. Several products are now available that purport to reduce infection and inhibit thrombosis.

Neutrolin (CorMedix, Berkeley Heights, NJ) is a catheter-lock solution composed of a proprietary formulation of taurolidine 1.35%, citrate 3.5%, and heparin 1000 units/ml. The LOCK-IT-100 study, which enrolled 805 patients from 70 sites in the United States,

was completed in mid-2019, and showed that Neutrolin significantly reduced catheter-related bloodstream infections. The primary end point was the risk of catheter-related bloodstream infection (CRBSI). There were 9 CRBSIs for patients in the Neutrolin group compared with 32 CRBSIs for patients in the heparin group: a 71% reduction in CRBSIs. Secondary end points, catheter removal or loss of patency, showed no statically significant difference.[51] With these findings, the FDA awarded Neutrolin fast-track status and qualified infectious disease product designation. The company, CorMedix, is working with the FDA to obtain approval for commercial distribution in the United States. The product is available for use in Europe.

ClearGuard HD (Pursuit Vascular, Maple Grove, MN) Antimicrobial Barrier Cap is another product marketed to reduce CVC infection. It is used in a similar manner to a standard CVC cap, but the ClearGuard has a rod and threads containing a dry chlorhexidine coating. Once attached to the catheter hub, the chlorhexidine dissolves into the lock solution promixal to the catheter clamp, killing almost 100% of common pathogenic organisms.[52]

A third option to reduce CVC infection is the TEGO (ICU Medical, Inc., San Clemente, CA) HD connector,[53] which creates a closed system that needs to be changed only once weekly. Each connector is made up of 2 components: an internal body and an outer silicon sheath. A TEGO connector is attached to each hub of the CVC, creating a microbiologically closed system. Dialysis lines are attached to the connector in an aseptic technique. The product affords less manipulation of the catheter, yielding less opportunity for bacterial contamination. The connectors are commonly used with Curos disinfecting port protectors (3M, St. Paul, MN).

A recent study by Brunelli et al.,[54] comparing ClearGuard with TEGO, plus Curos showed that ClearGuard had a rate of CRBSI significantly lower than TEGO plus Curos.

Conclusion

Access for HD remains a complex problem that still needs to be solved. Many avenues of investigation have been explored, enhancing the creation, maturation suitability, and durability of the access. The data presented here are promising; however, a clear path has not yet been found. We need to continue our diligence and resolve to optimize care and quality of life for those patients who have no choice but to proceed with long-term HD.

DISCLOSURE

MVD is the Medical Monitor for the phase 3 ACCESS Trial, a clinical trial evaluating the effectiveness of sirolimus. All the other authors declared no competing interests.

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