Bioengineered Arteriovenous Grafts

The recent transition to clinical use of both allogeneic and autologous tissue-engineered vascular grafts represents a significant evolution in hemodialysis access.

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The use of polytetrafluoroethylene grafts for hemodialysis access, as first reported by Scribner in 1960, revolutionized the care and treatment of patients with chronic kidney disease (CKD).[1] Five years later, the introduction of the Brescia-Cimino fistula dramatically improved outcomes and transitioned kidney failure to a disease that could be routinely managed for long-term survival.[2] Somewhat remarkably, nearly 50 years later, these two approaches still form the foundation of hemodialysis access. Although there have been some notable scientific innovations (eg, the HeRO catheter [Hemosphere, Inc., Eden Prairie, MN] and heparin-bound Propaten vascular graft [Gore & Associates, Flagstaff, AZ]), the long-term performance of hemodialysis access shunts is abysmal when compared to other cardiovascular reconstructions. From an economic perspective, despite new treatment guidelines (ie, Fistula First and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative) and new insurance reimbursement strategies, the costs associated with hemodialysis access continue to rise.

The high failure rate of both fistulas and grafts is due in large part to the mechanical challenges associated with supraphysiologic hemodynamic loads and repeated needle puncture. Infection facilitated by frequent needle stick is another major problem, particularly for synthetic grafts. It is also important to note that fistulas and most

Figure 1. Endovascular delivery of the Lifeline TEVG (Cytograft Tissue Engineering, Inc., Novato, CA). The Lifeline graft exhibits burst pressures in excess of native vessels, with a wall thickness < 200 µm thick. The graft is extremely flexible and can collapse well within a catheter-based delivery system. In this case, a 4.8-mm graft is mounted on a 6-F catheter with a 7-mm balloon and is encapsulated within a sheath that gives a total crossing profile of < 11 F (left). The graft tissue, removed from the catheter, is shown collapsed (center) and mounted to the manufacturing mandrel (right). This may be an enabling device for existing percutaneous bypass technologies for both the lower limb and coronary applications, with smaller-diameter grafts being delivered in significantly smaller sheaths. Although percutaneous delivery of an arteriovenous access graft is also possible, the tunneling requirements and the thicker wall required to support immediate puncture (approximately 500 µm) negate most of the benefits normally associated with percutaneous delivery.

grafts are encumbered by the necessity to have a second access option (typically a temporary catheter) for 3 to 12 weeks while the permanent access matures. Roughly 30% of fistulas fail to mature, and catheter-related complications during maturation represent a significant fraction of the overall hemodialysis access maintenance cost.[3] The quest for a synthetic biomaterial that is antithrombogenic, compliant, and resistant to infection and puncture-related failures remains unrealized despite more than 50 years of materials research.

In 1986, Eugene Bell introduced the concept of a cell-based, bioengineered vascular conduit and gave rise to the field of cardiovascular tissue engineering. In theory, a tissue-engineered vascular graft (TEVG) could be built to withstand supraphysiologic hemodynamic loads, heal and remodel in response to needle puncture, and be more resistant to infection than synthetic grafts. Moreover, these TEVGs could be punctured immediately without a postoperative maturation phase and would improve compliance to decrease turbulent flow and distal stenosis. For the last 25 years, this vision has been widely held as the "Holy Grail" of vascular surgery, but like many regenerative medicine technologies, this pioneering vision proved more difficult in practice than in theory. TEVGs remained an academic exercise until 2001, when Shin'oka and colleagues reported a clinical study using a cell-seeded resorbable polymer ringlet to reconstruct congenital defects in the pulmonary outflow tract of four pediatric patients.[4] Although this application was limited to the low-pressure pulmonary setting, the first clinical use of a TEVG remains a landmark achievement in the field of cardiovascular tissue engineering.

In 2007, our group reported the first human use of a TEVG in the high-pressure circulation, implanting a completely biological and autologous tissue-engineered hemodialysis graft into six CKD patients.[5,6] Encouraged by these clinical successes, the field has continued to grow. In 2010 alone, there were more than 75 independent laboratories that reported preclinical or benchtop results with a TEVG. Dozens more published supporting research with TEVG as a key word, addressing topics with direct relevance such as the recruitment of endothelial cell precursors to the lumen or bioreactor design. A detailed description of these studies is beyond the scope of this article, but the field is reviewed in detail elsewhere.[7] In this article, we focus on an update of clinical use of TEVGs for hemodialysis access and briefly discuss the likelihood of widespread adoption of this approach in the future.

TEVGs IN HEMODIALYSIS ACCESS

To date, this biological TEVG, called the Lifeline graft, remains the only tissue-engineered graft that has been used clinically in the high-pressure arterial circulation. This graft is unique in that it is built without any sort of exogenous biomaterials to provide mechanical strength. We believe that the absence of synthetic biomaterials is one of the keys to the long-term efficacy we have observed. The inclusion of synthetic biomaterials (even resorbable polymers) is linked to various inflammatory responses that can hinder cell functionality.

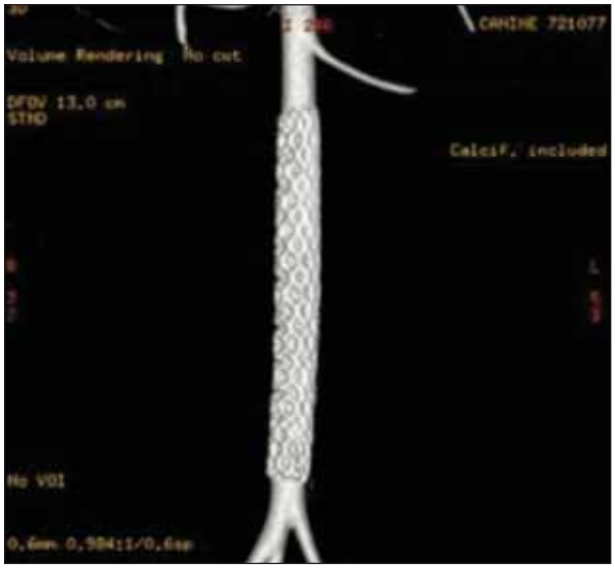

Figure 2. A Lifeline stent graft deployed in the abdominal aorta in a canine model. Three months after deployment of the stent graft via the femoral artery, the device continues to exclude an aneurysmal defect without complication.

In our initial clinical cohort, all patients had been on hemodialysis for at least 4 years and represented not only the "worst of the worst" cases from a clinical perspective, but also from a cost perspective. Indeed, these patients were averaging roughly three interventions per patient-year in the 12 months immediately before implantation. In the phase I/II clinical trial with autologous TEVGs, we observed a 4.2-fold reduction in event rate relative to preoperative performance with the standard of care. This reduction in event rate is particularly noteworthy in that complication rates typically increase dramatically for patients at later stages of CKD. With our longest-surviving patient, we have observed 3-year primary patency rate with no complications in a graft that has been punctured nearly 1,000 times. By contrast, the same patient had three graft failures and a total of 10 interventional events in the 24 months immediately before implantation of the Lifeline graft. Clearly, this example represented our best outcome, but the reduction in event rate was evident for every patient with a graft that matured for hemodialysis access.

As we transition to a second-generation allogeneic version of the Lifeline graft that is available to clinicians "off the shelf," we have observed similar results. A phase III clinical trial comparing the allogeneic Lifeline graft to an expanded polytetrafluoroethylene graft in a broader spectrum of hemodialysis patients has been initiated.

During the next 2 years, it is likely that two other groups will transition to clinical studies with a TEVG used as an arterial implant. Dr. Shin'oka continues to improve the mechanical properties of his cell-seeded polymer, suggesting that recent devices may withstand arterial pressure in a clinical setting. Similarly, Humacyte, Inc. (Morrisville, NC), a company using a derivative of Dr. Shin'oka's approach, has shown impressive preclinical results with cadaveric smooth muscle cells seeded into a resorbable polymer.[8] There are significant challenges associated with the scale-up of this TEVG (a large number of cadaveric donors are required to be pooled to produce a relatively small production run, which poses major cost and regulatory hurdles); however, the group has recently reported an approach using bone marrow seeded into the resorbable polymer. This latest generation of technology has the potential to be both clinically and commercially viable.

KEYS TO CLINICAL ADOPTION OF TEVGs

As TEVGs transition to clinical use, the clear question is whether these devices will achieve widespread clinical adoption or be limited to niche applications, such as chemically modified biological grafts (eg, Artegraft [Artegraft, North Brunswick, NJ], ProCol [Hancock Jaffe Laboratories, Inc., Irvine, CA], and SynerGraft [CryoLife, Inc., Kennesaw, GA]). Early efficacy results from our own clinical trials are encouraging, and there appear to be intrinsic advantages to these biologic grafts. However, one of the critical challenges associated with commercialization of TEVGs is demonstrating cost effectiveness.

Tissue-engineered products are extraordinarily costly to produce due to demanding environmental controls, lengthy culture periods, expensive reagents, and stringent lot release testing associated with quality control requirements. Even our third-generation TEVG (a woven allogeneic graft) requires at least 3 weeks in total manufacturing time, and we anticipate a price premium relative to expanded polytetrafluoroethylene grafts of at least $4,000. First- and second-generation grafts, which require significantly longer culture periods, may require a nearly $10,000 cost premium. Humacyte's TEVGs are faced with similar challenges given the 8-week culture period, extensive donor screening, and the lot release testing associated with pooled cadaveric donor cells. This cost premium presents a clear barrier to entry for

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TEVGs in the current reimbursement environment. However, with the average intervention to maintain a hemodialysis access at approximately $8,500, a reduction of one to two events over the life span of the TEVG would suggest cost effectiveness relative to the standard of care.[9]

It is also important to note that these novel devices will initially be targeted at later-stage patients or those who have shown poor tolerance for synthetic grafts. These patients tend to have exponentially increasing intervention rates and are disproportionately more expensive to manage. The cost-effectiveness hurdle is significantly easier to navigate in this patient population, which can typically experience three or more graft-related events per year. Given the dramatic reduction in event rate we have observed in phase I/II trials with both our first- and second-generation devices, this cost-effectiveness goal would seem well within reach, particularly for the off-the-shelf allogeneic TEVG.

ENDOVASCULAR APPLICATIONS FOR TEVGs

TEVGs may also be uniquely suited for endovascular applications. For example, the Lifeline graft exhibits extremely high mechanical strength with a very thin, flexible wall (Figure 1). This combination of mechanical properties allows the graft to compress well for endovascular delivery. Although the idea of a biologic stent graft is not entirely new (pericardium and small intestine submucosa have been previously proposed), the Lifeline graft demonstrates a significantly smaller crossing profile than biologic precedents. Moreover, as we have shown with the TEVG, this human-derived, biologic approach is antithrombogenic, resistant to infection, and lacks chemical modification or cells that might initiate an immune response. These intrinsic material advantages coupled with the positive handling properties suggest that the Lifeline stent graft may play a role in the expanding number of indications that can be treated with an endovascular approach.

We have shown excellent durability and patency with the Lifeline stent graft in large animal models, treating both abdominal aortic aneurysm defects and peripheral arterial occlusions via a femoral arterial approach. With time points beyond 3 months in both models, the out-

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look for this minimally invasive delivery strategy is promising (Figure 2). We consider this endovascular platform to be at least 2 years from first-in-man studies, but it is clear that the benefits of tissue engineering are not limited to open surgical repair.

CONCLUSION

Twenty-five years removed from Bell's pioneering study with laboratory-grown blood vessels, the clinical era of TEVGs is upon us. Cell-based grafts, which are free from branches, lesions, or immune stimulating components, may finally provide a vascular prosthesis that matches the efficacy of native tissue. Indeed, the results from our own phase I/II trials would seem to suggest that the TEVGs can perform better than arteriovenous fistulae by improving patient outcomes and decreasing overall maintenance costs. However, whether these engineered arteries will significantly affect hemodialysis access on a widespread basis will be driven in large part by cost-effectiveness studies. With our own phase III clinical trial studying an allogeneic, second-generation device underway, the answer to this exciting question will be evident within the next 18 months. ■

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