

CARDIOVASCULAR DEVICE UPDATE

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Alternative materials offer surprising new options vs. stenting

By MARK McCARTY CDU Washington Editor

As the current debate over the safety and efficacy of drug-eluting stents demonstrates, veins and arteries aren't simply plumbing – or at least not the kind of plumbing that can be fixed in a one-fix-fixes-all strategy. And patients with end-stage renal disease (ESRD) are in a similar but less critical situation with regard to the continued viability, or patency, of their veins and arteries.

Makers of drugs, devices and biologics are all interested in vascular patency, and the current research on novel products to create and maintain vascular patency indicates that help may arrive in the near future with the use of innovative alternatives to stenting.

Among these strategies is the use of a novel combination of products. And another employs good old-fashioned medical gases to relieve the stresses on blood vessels and keep them open.

Structural integrity

Pervasis Therapeutics (Cambridge, Massachusetts) is approaching this problem with the use of mechanisms already present in the human body, a combination of human cells and collagen. The company's product is Vascugel, engineered to bolster the structural integrity of arteries and veins for patients undergoing dialysis. It is recruiting patients for a pair of Phase I clinical trials that will look at how well Vascugel reduces the proliferation of smooth muscle cells and fibroblasts for both modes of arteriovenous access – access grafts and fistulas.

According to Steve Bollinger, president of Pervasis, Vascugel is not a stem cell product but is "extracted from endothelial cells in the aorta. And he pointed out that growing cells from the patient's own aorta is "a logistical and manufacturing challenge."

For instance, the fact that these cells are allogeneic suggests the possibility of an immune system reaction. Thus, Pervasis scientists shield the endothelial

cells from the immune system by growing the cells in a matrix of a refined, off-the-shelf collagen. In use, Vascugel is applied to the outside of the blood vessel, and the harvested endothelial cells secrete several substances that work their way past the outer two layers of the blood vessel, the adventia and the media, into the inner layers of the blood vessel.

Among the substances provided by the transplanted endothelial cells is heparin sulfate, an artificial version which is one of the most potent clot-busters currently available. However, endothelial cells also produce a chemical that controls fibroblast growth as well. The damage done to the endothelial lining during dialysis may be repaired, fittingly, by donated endothelial cells.

"What our animal models told us is that this technology takes the vein back to its natural state. As long as it is not retraumatized, the treated blood vessel will remain patent for quite a long time — for months, maybe even years," Bollinger said.

Applications designed for better blood flow

Pervasis was founded in 2003 with the mission of "aiding vascular disease and restoring natural blood flow to critical organs," Bollinger said. The basic research behind Vascugel was initiated roughly a decade ago by one of the company's founders, Elazar Edelman, PhD, now the head of the Harvard-MIT Biomedical Engineering Center (Cambridge, Massachusetts).

The company is exploring applications for using Vascugel to treat peripheral as well as central vascular disease, such as diabetes, but "trauma is another place where we'd like to go," said Bollinger. And the company is exploring the possibilities for using Vascugel in conjunction with coronary artery bypass.

Researchers at Pervasis have no data yet as to whether Vascugel's efficacy improves with repeated application, but Bollinger said the company believes it is possible "to keep repairing the body indefinitely." But to firmly establish whether this is indeed the case, "[w]e need a lot more human data to figure out how the human body deals with it time and time again."

Bollinger would not project sales of Vascugel as a treatment for ESRD or for other indications but said that dialysis patients may be the first to benefit if clinical trials demonstrate efficacy.

"I think patients will embrace this," he said, adding that doctors are concerned about repeatedly repairing blood vessels. "They're desperate for a fix" for this problem, he added. And he said the company's officers and board members see large promise in the therapeutic opportunities for this combination product.

Time to market — time to reimbursement

Time to those opportunities is always a concern for small, capital-intensive ventures, and Pervasis is no different. Bollinger said that depending on how clinical trials move along, "I'd like to see this in the market by 2009, maybe late 2008 if possible," with applications in dialysis the first target.

Reimbursement is another area in which the company expects success, given that an estimated 300,000 patients with end-stage renal disease (ESRD) require dialysis. Medicare data suggest that about one in four of these end up with vascular access problems, running up a Medicare tab of \$1.5 billion annually.

Bollinger said he is confident that Pervasis will get a favorable national coverage decision from the Centers for Medicare and Medicaid Services for use on dialysis patients. The development plan for Vascugel "will probably be a staged-in program," he said. Pervasis intends to overlay upcoming studies for other uses, some of which will have to address only efficacy "because we'll have proved safety."

Bollinger indicated that financing is in good hands and that to date, the firm has no plan to go public. "We have quite a dream team, made up of three very large VC firms," including Polaris Ventures (Waltham, Massachusetts), Highland Capital Partners (Lexington, Massachusetts) and Flagship Ventures (Cambridge, Massachusetts). On the other hand, he would not rule out the possibility of going public at some point in the future.

Firming up xenogeneic use

As for future development of Vascugel, Bollinger said Pervasis is interesting in "looking at anyplace where the plumbing doesn't work very well," but that Vascugel probably never will serve as primary treatment for congestive heart disease. Rather it will most likely be used as an adjunctive treatment.

As Pervasis works to take Vascugel to market, Edelman is pursuing endothelial inflammation and proliferation farther down the xenogeneic track. In a paper published in the July 4, 2006, edition of *Circulation*, Edelman and Heiko Methe, MD — who is also employed by the Harvard-MIT center — discuss the results of an experiment on mice using porcine endothelial cells to evaluate the immune response to matrix-embedded cells after sensitizing the rodents' immune systems to the swine cells.

The authors note that previous experiments demonstrated that implantation of such cells in mice that were not immunologically sensitized did not trigger an overwhelming immune response, but such experiments did little to clarify whether serial treatment is possible.

Provocation deliberate

The authors say also that the deliberate provocation of the immune system was included in the experiment partly in order to examine "the influence of heightened anti-endothelial immunity that is a common clinical feature in a variety of autoimmune and endocrinologic diseases," including diabetes mellitus (as opposed to diabetes insipidus, a hypothalamic and/or pituitary disorder) and hypertension.

The article also hints at a strategy for future research in this area. Edelman and Methe write that "heightened anti-endothelial immunity has been identified as a pivotal rate-limiting effect for EC-based therapies," suggests that "a more detailed understanding of how EC phenotypic shifts occur in vascular pathology . . . would be of great benefit in developing appropriately targeted therapies."

Gases another aid to patency

Another research effort exploring an alternative material suggests another way that surgeons may be in a position to intervene in the formation of new endothelial tissue as the result of surgical intervention. The July 2006 edition of the *Journal of Vascular Surgery* describes a study conducted by Kathleen Raman, MD, et al., at the department of surgery at the University of Pittsburgh (Pittsburgh, Pennsylvania), investigating how carbon monoxide and nitric oxide gases might be used to inhibit hyperplasia of the intima — the lining of the inside of blood vessels — when used together. The authors state that both gases "possess vasoprotective properties."

Existing studies in small and large animals show that nitric oxide (NO) inhibits intimal hyperplasia, but carbon monoxide (CO) has been studied only in rodents. The authors state that there is evidence that "these two molecules may exert their vascular effects through common as well as unique signaling pathways," but the abstract provides no further detail on that comment.

The team split the animal subjects (pigs) into four groups, two of which received only CO. One of these two received CO before and during surgery and the other only before surgery. Of the third and fourth groups, only one received the pre- and perioperative CO, but both received NO synthase (iNOS transfer) in one iliac artery and an adenovirus-delivered version of vascular endothelial growth factor, known as AdlacZ, in the opposite iliac artery.

Elevation 'modest and transient'

The pigs that were treated only with CO for one hour before angioplasty experienced a "modest and transient" elevation in carboxyhemoglobin and a reduction in the total area of new intimal tissue of about 25%.

The ratio of intimal area to medial area three weeks after the operation was down 10% as well. Those numbers dropped to 51.7% and 31%, respectively, with the double dose of CO. No evidence of toxicity showed up at the dose of 250 parts per million of CO.

As for the pigs that received the NO treatment, the researchers indicate that the AdlacZ "did not further increase the inhibitory effect of CO on intimal hyperplasia," but that "the combination of inhaled CO and iNOS gene transfer resulted in greater protection," showing up with a 64% reduction in new intimal tissue area and a 48% drop in the ratio of intimal-to-medial diameter.

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