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The Science Behind Local Drug-Delivery Technologies: The Benefit of Sustained Paclitaxel Release in the SFA

Sustained drug release is key to maintaining biological effect.

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The biological composition of peripheral atherosclerotic lesions is more complex than in the coronary territory. In peripheral atherosclerotic lesions, the disease burden is higher and the presence of total occlusions and calcium is more prevalent. Consequently, clinical studies consistently demonstrate that after percutaneous intervention of peripheral lesions, the restenotic process is not only more aggressive but also peaks later compared to coronary lesions.[1] In a retrospective analysis looking at nearly 600 patients who had undergone successful endovascular therapy for superficial femoral artery (SFA) lesions, Iida et al determined that restenosis peaked at approximately 12 months.[1] This is different from the coronary territory, where restenosis tends to peak at approximately 6 to 9 months. In developing a new technology for peripheral vascular applications, a durable biological effect can only be achieved if sustainable therapeutic levels of drug are maintained during this critical period.

THE ELUVIA STENT MECHANISM OF ACTION

The Eluvia Drug-Eluting Stent (Boston Scientific Corporation) utilizes a polymer drug combination designed to sustain arterial tissue concentration of paclitaxel at a therapeutic dose for beyond 1 year. Polymer-based local drug delivery is a well-established technological approach that has been thoroughly tested in the clinical setting over the last 20 years. The advantage of a polymer-based approach is that the amount of drug delivered to any given area can be accurately controlled over time. Eluvia's pharmacokinetic profile is unique in that a controlled burst of drug is initially released followed by a sustained release of a lower dose of drug that is maintained within therapeutic levels over the first 12 months after implantation (Figure 1). Another notable difference compared to other paclitaxel-based delivery systems is that Eluvia's elution profile is designed for the drug to never exceed the levels of potential vascular toxicity.

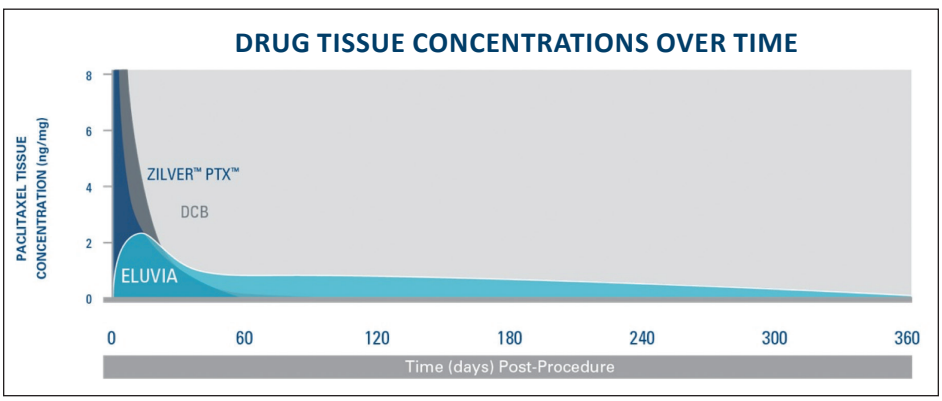

Figure 1. Scheme depicting the pharmacokinetic profile of Eluvia versus Zilver PTX (Cook Medical) paclitaxel release over 12 months based on preclinical pharmacokinetic analysis. Data for Eluvia on file at Boston Scientific Corporation. Data for Zilver PTX available from Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX stents—evaluation of pharmacokinetics and comparative safety in porcine arteries. J Vasc Interv Radiol. 2011;22:603-610.

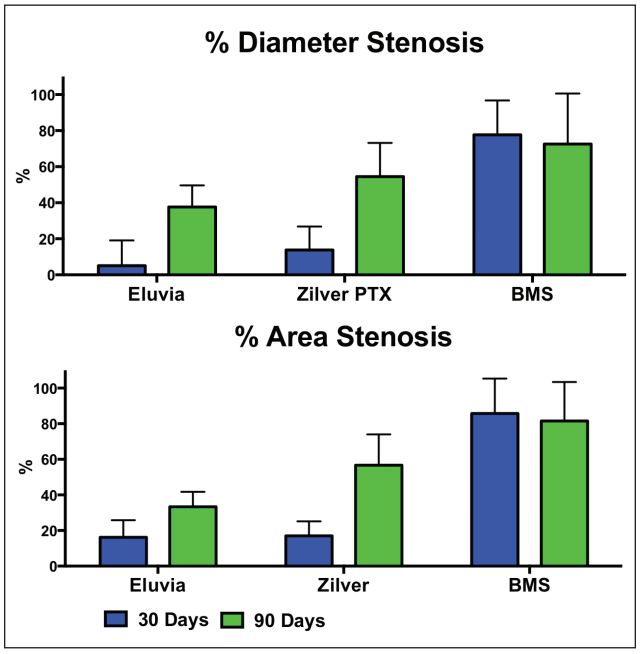

Figure 2. Percent diameter stenosis (angiography, top) and percent area of stenosis (OCT, bottom) change from 30 to 90 days after stent implantation.

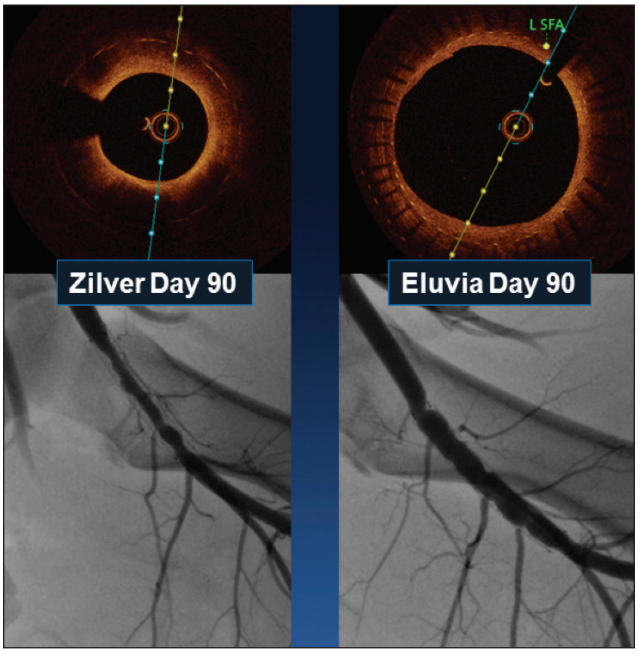

Figure 3. Representative angiographic and OCT images at 90 days in both drug-eluting stent groups.

TRANSLATIONAL FINDINGS

The effect of Eluvia's sustained drug release on neointimal formation was recently evaluated in a head-to-head experimental study using a porcine model of peripheral atherosclerosis. For this study, we utilized a unique strain of swine with familial hypercholesterolemia (known as FH-swine). This strain of swine exhibits high levels of low-density lipoprotein (LDL) and develops spontaneous atherosclerosis due to a naturally occurring LDL-receptor deficiency. This model allowed us to study the natural evolution of restenosis in an accelerated disease model, which more closely reflects what is actually happening in the clinical arena. The model has also allowed us to study and compare the effects of several antirestenotic therapies in restenosis prevention after vascular intervention. In this study, three test groups were included: a polymer-based paclitaxel-eluting arm (Eluvia), a polymer-free paclitaxel-eluting arm (Zilver PTX), and a bare-metal stent control arm. This allowed us to study the impact of two different paclitaxel-eluting methods in restenosis prevention and vascular healing (Figure 2).

Multimodality imaging including optical coherence tomography (OCT) and quantitative vascular angiography was performed at 30 and 90 days. Histological evaluation was performed and compared to the imaging findings. At 30 days, both Eluvia and Zilver PTX showed similar behavior in terms of stenosis reduction compared to the bare-metal stent group. The mean percent area stenosis by OCT was comparable between both groups (approximately 16%–17% in both groups). However, at 90 days, important differences in neointimal proliferation were seen between both devices. Although the degree of intrastent stenosis remained stable in the Eluvia arm between 30 and 90 days (approximately 10% reduction in lumen area; Figure 3), the Zilver PTX arm seemed to experience higher levels of neointimal proliferation with a lumen area reduction of approximately 47%. Neointimal proliferation rates measured in vivo (OCT) and ex vivo (histology) correlated and confirmed these differences seen in both devices.

CONCLUSION

In summary, in an experimental model of atherosclerosis, the polymer-based sustained release of paclitaxel provided lower levels of neointimal proliferation compared to a polymer-free stent-based control. ■

1. Iida O, Uematsu M, Soga Y, et al. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. Catheter Cardiovasc Interv. 2011;78:611-617.

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Disclosures: The Skirball Center for Innovation has worked with most vascular drug-eluting device manufacturers.