What's Next in Drug-Eluting SFA Technology?

Juan Granada, MD, discusses potential next-generation advancements in drugs, delivery methods, and study.

WITH JUAN F. GRANADA, MD, FACC

How would you characterize the current state of drug-delivery devices available for use in the superficial femoral artery (SFA)?

Our first experience with drug-delivery platforms was in the coronary arteries, where the success with drug-eluting stents (DESs) has been so significant that it is unlikely the market will revert to favoring non–drug-eluting solutions. The improved patency and clinical outcomes observed with local drug delivery ushered in a new era in the superficial femoral and popliteal segments as well, although bare devices continue to have a role.

The SFA also poses unique challenges related to biomechanical forces and lesion length and composition. Whereas stenting still dominates coronary intervention, the desire to leave nothing behind is often a deciding factor in SFA device selection, creating a substantial role for drug-coated balloons (DCBs). However, one potential downside of a balloon-only approach is that depending on the complexity of the disease, a percentage of these patients will cross over to stent placement as well. Some interventionalists will elect for a DES in these cases, feeling that why not place a stent as a primary strategy if they will likely need to place one anyway. Similarly, the disadvantages of implantable devices become apparent if they fail, at which point the next therapeutic options are limited due to the permanent implant being in place.

The bottom line is that both types of devices have shown improved performance over their bare counterparts in clinical trials in both safety and efficacy. The decision as to which to choose is up to the operator based on the patient and lesion characteristics.

Aside from cases in which a permanent scaffold is determined to be necessary, how would you summarize the current questions that DCBs must address?

Looking back, the first question DCBs needed to address was whether a single drug application would work. Next, we looked at safety—the potential for embolization and downstream effects. After that, clinical outcomes in randomized controlled trials had to show superiority over uncoated balloons out to 1 year. Now, it comes down to sustainability of the treatment effect—how long can we maintain the favorable effect of the antirestenotic drug. We're talking about a highly aggressive disease profile that shows a rate of lumen loss that increases over time. Now, we will further explore the abilities of each individual platform to maintain this effect over 3 to 5 years and determine which drug, dose, and excipient/carrier profiles yield the best outcomes for the longest periods.

What do you predict will be the next stage of evolution for paclitaxel-coated balloon platforms?

All the current DCB platforms are based on paclitaxel delivery, so I think we will continue to see new iterations in dosing and coating features with a goal of maintaining higher therapeutic tissue levels as long as possible using as little drug as possible. This will be particularly important in below-the-knee applications or in SFA cases involving critical limb ischemia.

What can you tell us about the excipients in use and any potential for innovation with those in particular?

Excipients are molecules that attach to and carry paclitaxel into the vessel wall, and they are key for DCBs. The paclitaxel acquired by all the device manufacturers is mostly in a solid-phase form. The paclitaxel is processed, solubilized, and mixed with excipients. In this process, the capacity to bring the paclitaxel to the vessel wall may increase, but the solubility may also increase; therefore, the levels of paclitaxel in the tissue levels may decrease more

rapidly. An excipient is important because it brings balance between coating solubility and tissue levels over time.

Today, most companies are likely not looking to invest in discovering new excipients and are instead focusing on refining the current options. There are many opportunities to fine-tune the coating to increase durability and improve the pharmacokinetic profile.

What is next on the horizon for DESs?

The next question to be addressed will be the utility of polymers in binding the drug to the stent. The Zilver PTX paclitaxel-eluting stent (Cook Medical) has demonstrated long-term outcomes superior to bare stents and was the first to market. The Eluvia platform (Boston Scientific Corporation) is not yet available in the United States but has gained approvals in Europe. The two platforms differ both in the design of the metallic stent, but also the presence or absence of a polymer to bind the paclitaxel to the stent. The Zilver PTX does not incorporate a polymer, whereas the Eluvia does. The goal of a polymer-based approach is a more controlled-release profile that would ultimately maintain therapeutic tissue levels for a longer duration. The effectiveness of both DES designs will be tested in the ongoing IMPERIAL trial, which will randomize them head to head.

In the SFA, the DESs placed are often particularly long in order to cover the long, diffuse disease encountered in this segment. Ideally, the next wave of innovation in DESs will see a decrease in the amount of surface area the devices cover, thereby decreasing the amount of permanent components left behind. A reduction in polymeric mass and the introduction of bioresorbable polymers are also a possibility. The key will be to continue to provide long-term scaffolding without compromising the integrity of the implant in a challenging biomechanical environment.

What do you see as the potential for fully bioresorbable DESs in the SFA?

The field of bioresorbable technologies has been constantly evolving, but their introduction into the peripheral field has been delayed by the biomechanical challenges specific to the peripheral vascular territory. It took nearly 2 decades for metallic stents to become stable structures in the SFA, and there is a lot of apprehension that due to the biomechanical challenges, bioresorbable devices will break and fail in these territories. This hesitation is why the movement toward the use of bioresorbable technologies in the SFA has not been as aggressive as in the coronary territory, where there have also been setbacks as well as progress.

However, in areas with less biomechanical motion, such as the proximal SFA, the iliac artery, and in below-the-knee applications, there is potential for bioresorbable technologies to accomplish the desired outcome of providing a scaffold-based drug delivery followed by total disappearance of the implant. Second-generation polymers and bioresorbable devices have the potential to be thinner, more durable, and are stronger than previous iterations, and I believe bioresorbable technologies may have a promising future in peripheral vascular interventions in the future.

What can you tell us about liquid-state paclitaxel and its applications?

Liquid formulations are certainly another new frontier for paclitaxel delivery. Today's drug-delivery platforms are based on solid-phase paclitaxel delivery, in which drug particles coating the balloon or stent are delivered into the diseased tissue. The behavior of these particles determines the pharmacokinetic profile of the platform.

With liquid-form paclitaxel delivery, the vessel would first be occluded to create a chamber around the diseased segment, with the objective of pressure-soaking the target area with paclitaxel. After a certain period of time, the nonabsorbed liquid paclitaxel is withdrawn from the chamber back into the system, with the target tissue having been treated without losing a significant amount of drug into the systemic circulation. Liquid-form paclitaxel could be particularly important for below-the-knee applications in which we do not want to lose a lot of paclitaxel downstream, especially in the presence of a wound.

As is the case with DESs and DCBs, there are advantages and disadvantages with every potential method. For example, the advantage of liquid-phase paclitaxel is that it can be used to treat very long diseased segments. The potential disadvantage to this method is that the mechanical obstruction of the stenosis within the targeted segment still needs to be addressed. As a result, a balloon- or stent-based intervention may still be required, and some interventionalists may initially choose one of these for a faster, more effective solution.

How do the "limus"-based drugs differ from paclitaxel, and what is the latest on exploring limus in the periphery?

Limus drugs are cytostatic, rather than cytotoxic, which means that the cell becomes inhibited from proliferation if therapeutic tissue levels are maintained over time. Conversely, paclitaxel is a cytotoxic drug, which means it essentially induces smooth muscle cell death and has potential for toxicity.

One important clinical difference between limuses, such as sirolimus, and paclitaxel/taxol derivatives is the fact that

sirolimus degrades relatively quickly once it is put into solution. So, once sirolimus is in the tissue, it remains bioactive for several days before it degrades, which requires the drug to be protected following drug release. On the other hand, paclitaxel is a very stable drug; it can be delivered into the tissue and stays there for a long time without much biological degradation.

The challenge with limus derivatives is the need for control-release mechanisms. Limus drugs must be protected from degradation and require long-term release and tissue levels. Therefore, some challenges still exist from a technologic viewpoint as to whether physicians can accomplish the same outcome using balloons with limuses compared to paclitaxel-coated balloons. Another technologic approach is trying to integrate percutaneous transluminal angioplasty dilatation and sirolimus delivery using polymer nanoparticles (Virtue, Caliber Therapeutics). By using this approach, sustained tissue levels of silrolimus are maintained via controlled polymeric release. In the other hand, if a permanent implantable device is used, such as a stent, the drug potentially can be encapsulated inside of a polymer, and a long-term delivery means could be created. Currently, it is fair to say that stent-based platforms have a higher chance to succeed using limus derivatives than a balloon would be.

Other than paclitaxel and the limus options, what other drugs are being evaluated for potential applications in peripheral artery disease?

Dexamethasone, a steroid and potent anti-inflammatory drug commonly used to treat conditions such as skin conditions and respiratory diseases, is currently being used by Mercator MedSystems with an adventitial delivery catheter. First-in-human studies have shown that dexamethasone has the potential to decrease restenosis after angioplasty when delivered into the adventitia. This is an important distinction—DCBs release drugs by passively placing a drug on the surface of the vessel. Then, the pharmacokinetic profile of the drug depends on the passive transfer from the surface of the vessel over time. DESs create a depot or a reservoir around the strut, and the drug is diffused into the tissue over time. With adventitial delivery, the drug is deposited entirely into the adventitia of the vessel and a depot is created deep into the vessel wall. Thus, the mechanism of delivery and type of drug are very important factors. For example, the water-soluble hydrophilic drugs could potentially be delivered directly with a needle but would be exceedingly difficult to deliver via DCB because they will get washed away with the flow.

What are some of the potential advantages and disadvantages of adventitial delivery?

The adventitial method of drug delivery has similar potential advantages and disadvantages to using liquid-phase pacliltaxel. Adventitial delivery can allow physicians to go deeper and treat a longer segment of the vessel, but it does not necessarily avoid the use of balloons or stents to manage the mechanical obstruction. Additionally, with adventitial delivery, as with any other local drug delivery device, it is possible to induce additional vessel injury caused by the mechanism of delivery itself.

How do you address emerging therapies in your preclinical testing work?

When developing a device with a new delivery method, a new dose concentration, or a new drug, the bioequivalence of the new concept should be compared with something we already know works clinically. In that way, experimental methodologies help us understand if a new technology has a pharmacokinetic behavior and profile and efficacy profile comparable to an existing device.

Once the pharmacokinetic and efficacy parameters are determined, technologies are validated using previously established protocols and methodologies accepted by regulatory authorities. In the 1990s, little experimental work was performed in the validation and approval of peripheral vascular devices. For instance, peripheral stents were approved by presenting coronary data for similar devices. Then, with the introduction of DCBs and DESs, the field evolved toward the development of dedicated SFA models for drug uptake and pharmacokinetics. Now, we are adapting some of these models to show the efficacy of these technologies compared to technologies that have been shown to work in the peripheral vascular territory in humans. In addition, we are entering a new era of calcium management, so there is increased interest in experimental models that show the impact of calcium presence on drug uptake and pharmacokinetics.

There is no question that experimental models are also evolving as the technology progresses. ■

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Disclosures: The Skirball Center for Innovation partners with multiple medical device companies in the validation of new technologies.