The Evolving Role of Preclinical Evaluation in SFA Therapy

Dr. Juan F. Granada discusses the current climate of preclinical research, lessons learned in evaluating drug-eluting technologies, common misconceptions, and what the future holds.

What is the current state of preclinical research in drug-eluting peripheral vascular technologies?

The focus and the scope of the research have changed from where it first began. At the beginning, it was all about efficacy—we didn't even know whether drug-coated balloons (DCBs) would work. There was a lot of skepticism regarding the ability to maintain a biological response with a single-dose application. However, over the last several years, the attention has shifted more toward safety and the effect of the drug concentration on the surface of the balloon. Now that clinical trials have shown the efficacy of these technologies in the superficial femoral artery (SFA), the focus has shifted toward the second-generation balloons in terms of the dose limit. Ultimately, the goal is to maintain efficacy but improve safety at the same time. We are also studying other possible applications for these technologies.

What would you say you've learned from the first-generation DCBs, and what would you predict for the second generation?

With the first-generation balloons, the efficacy observed has brought a lot of enthusiasm. Everyone was intrigued and excited to see that a single delivery without the presence of an implantable device could work. However, there were also concerns about vessel toxicity and the potential for embolization.

So, whereas the first generation of preclinical testing has focused on efficacy, in the second generation, there will be more focus on fine-tuning the drug dosage, safety considerations, and the use of this technology in other applications.

I think some of the current concerns are actually more hypothetical in nature, rather than linked to actual, relevant clinical effects. A better understanding of safety has the potential to help evolve these technologies into more sophisticated local delivery devices.

Have you noticed increased interest in your field of study from the vascular community at large as drug-eluting technologies have gained prominence?

From the very beginning, this field has been supported by a strong experimental foundation, and there is absolutely continued interest from the operators and clinicians to understand not only how the device works, but also the potential side effects that this technology may present in precarious areas.

How does the different anatomy of the peripheral versus coronary vasculature affect these clinical studies?

First, the biological response of a human peripheral artery is different than the biological response in the coronary territory, so we have to be very careful about interpreting the results from previous experimental studies. One of the main differences is obviously size. The size considerations entail larger areas with different biomechanical behavior (ie, significant torsion and different biomechanical stress). The other major difference is the reaction to the permanently implanted components. The vascular reaction to a stent in the peripheral artery is actually quite different than the coronary artery.

We must proceed with caution, as the data derived from coronary studies are difficult to extrapolate into the peripheral field and vice versa. More than ever, it is extremely important that preclinical studies are conducted in a similar way compared to the application of the device in the clinical setting. We must take all clinical factors into consideration when designing and evaluating preclinical models, such as whether predilatation or postdilatation are required or stents are placed, and it is vital that we properly evaluate results based on the design of the experimental study versus the clinical reality.

What are the particular anatomic areas of concern when testing drug-eluting technologies in the SFA, and how do they correlate with the preclinical arena?

In the SFA, the biomechanical properties and the mechanical stress on the device or treated area are very important. In humans, the primary area of concern is the distal SFA. When testing in animals, there is a hinge point near the hip in which the artery gets the maximal amount of torsion and deformation. It is extremely important to be careful about where the device is placed and to understand the impact of biomechanical stress on healing when using an implantable device. When it comes to testing, there are multiple variables we need to take into consideration; however, it is sometimes difficult to compare stents and balloons side by side in the same model.

What makes paclitaxel a good choice for applications in the peripheral anatomy? What other agents have the potential to be effective?

I would say that the field is broken into two main categories: the paclitaxel category and the limus category. Paclitaxel is the drug of choice right now because it works well. From the pharmacologic point of view, it is a very stable drug, and it doesn't degrade as much as limus drugs when they become soluble. Also, the high residency time that you see with paclitaxel is unparalleled. Once the balloon dilates the artery and the paclitaxel is attached to the vessel wall, it stays there, doesn't degrade, and essentially produces a long-term sustainable biological effect. By contrast, limus drugs tend to degrade once they are introduced into soluble form, so they need to be protected with more sophisticated and advanced delivery mechanisms.

Limus applications are attempting to encapsulate the drugs into dedicated delivery systems (ie, polymers or other carriers) to protect the drug from degradation and maintain tissue levels at that time. A few companies have achieved interesting biological results, and they have been able to show limus tissue levels up to 28 days, which is a big step forward in the field. However, these certainly require further clinical study.

What is one common misconception regarding preclinical testing, and how would you address it?

This is a very important question because it is critical to understand the limitations of experimental models as well as the limitations that clinical research sometimes carries. As we discussed, I believe experimental models show signals that may or may not be relevant for the clinical scenario. Conversely, in clinical studies, sometimes we do not see negative signals, but that doesn't mean they are not actually present.

One of the biggest misconceptions occurs when people disregard safety signals seen in experimental animal models. We have seen this over and over—experimental signals were described in the literature but disregarded, and clinical adverse effects were later found when these technologies were extrapolated to thousands of patients. We have to be cognizant and understand the value that the models actually bring to the table. What I always say is, if you find no biological response in terms of efficacy, that is okay. But if you find an adverse biological effect, it doesn't necessarily mean it's going to happen, but you do have to be very suspicious about the potential of an actual adverse event happening in clinical situations.

In a nutshell, people seem to have the basic misconception that these are just animal data, and animals are not like humans. That's a very common sentiment that I hear.

How has preclinical evaluation changed since your early days in the field, in terms of the testing you conduct? Which tests have gained more traction, and which are now seldom used?

I think the development of coronary drug-eluting stents helped a great deal with the development of innovative local delivery systems to peripheral technology. The basics of preclinical testing for local drug delivery systems have remained the same, but I think the methodologies have evolved. Nowadays, we see more sophisticated pharmacokinetic studies and drug-tracking studies. Computer modeling is also being used in the local drug delivery field, as well as a lot of complex and sophisticated immunostains for determining the presence of drug and the biological effect of different compounds in the arterial wall.

When it comes down to regular studies, the core of the regulatory work remains the same, but I really think the field has evolved in understanding the implications

of drug delivery in vessel healing and biological response in a very high level of detail.

What do you predict for the near future of pathology and preclinical testing in the peripheral vascular field? Is it growing, and if so, in what ways?

In general terms, it remains stable. What I've observed for the longest time in regulatory and clinical sciences is that they have been seen as a way to check a regulatory box in order to get a device approved for human patients. But I've seen a transition in the last 5 to 7 years in which companies now want to understand more and more about the biological effect of the device in terms of the safety and efficacy, mainly due to the fact that this is what clinicians want to know. This may have been driven more by marketing efforts rather than real research demands, but regardless, understanding the mechanism of function of these devices will help produce better devices.

I think this field has grown slowly and steadily, and I don't foresee a massive growth in experimental studies or the desire to do experimental research, but I do see that companies have migrated from the "me too" studies into more complex mechanistic studies, which is very refreshing. ■

Juan F. Granada, MD, FACC
Executive Director and Chief Innovation Officer
Cardiovascular Research Foundation Skirball Center for Innovation
Orangeburg, New York
Assistant Professor of Medicine
Columbia University College of Physicians and Surgeons
New York, New York
(845) 290-8100; jgranada@crf.org
Disclosures: The Skirball Center for Innovation partners with multiple medical device companies in the validation of new technologies.