The Role of Preclinical Data in Drug-Coated Balloon Therapy

Drs. Virmani and Granada explain the importance of preclinical data, discuss key parameters for evaluation, and review the science behind clinical performance.

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ROLE OF PRECLINICAL SCIENCE

What can we learn from preclinical data?

Dr. Virmani: Preclinical data play a very important role, not only to evaluate safety, but also to understand toxic and biologic effects. Classically, in clinical studies you evaluate, "is it reducing the percent of neointimal stenosis?" This does not always apply to the preclinical work, because animals lack the atherosclerotic process. Preclinical data do, however, tell us about safety of DCBs—specifically if there is an inflammatory reaction. For paclitaxel, preclinical evaluation can determine: Is this toxic? Does toxicity relate to the level of drug we are putting in? Does it lead to thinning of the media? Does it lead to an aneurysm? In the case of DCBs, it is very important to know if we are seeing drug effects at 28 days, such as deposition, fibrin, and delayed healing. You also have to take into consideration that we are assessing juvenile animal models, not humans who are older (aged > 60 years) with peripheral vascular disease. So, at 28 days in humans, you will not see complete healing. Instead, you might see endothelialization on the surface, and below you may have very few smooth muscle cells.

Dr. Granada: In the era of local drug delivery, experimental device validation has become extremely important in understanding the basic principles of the technology and the potential benefits and challenges of the technology before it enters clinical testing. In DCBs, experimental research answers questions about the impact of coating on tissue pharmacokinetics and biological effect.

Why are preclinical data so important in the landscape of DCBs?

Dr. Virmani: In the landscape of DCBs, you also want to know about distal emboli and how drug dose affects drug delivery. DCBs attempt to deliver a large amount of drug in a very short time, typically 60 seconds to, at most, 3 minutes with balloon inflation. The IN.PACT™ Admiral™ DCB (Medtronic, Inc.) carries a 3.5-µg/mm^2 dose of drug, whereas Lutonix (Bard Peripheral Vascular) carries a 2-µg/mm^2 dose of drug. Drug dose and delivery may make a difference, but it is also important to ascertain how quickly the drug needs to be delivered, the time from entering the system to placing the DCB in the artery wall, and if emboli are produced in distal beds. These are things that we can evaluate in animal models that we cannot easily learn in humans.

Dr. Granada: DCBs perform very differently compared to other local drug delivery technologies, as they aim to initially transfer drug "only once" via balloon dilatation but, at the same time, maintain drug levels in tissue over the long term. With experimental research, we were able to prove that first-generation DCBs were able to maintain tissue levels up to 90 days, which was an extremely important finding to validate the technology. Based on these findings, we were able to standardize the methodologies for DCB testing, and more importantly, we were able to determine the efficacy and safety boundaries of the technology through pharmacokinetic and tissue healing studies.

How does preclinical science relate to or work in partnership with clinical evidence?

Dr. Virmani: You look at the biology in the animal, whether healing is taking place and how quickly, as assessed by the location and quantity of fibrin, and if the drug is solid phase and how long drug persists in the arterial wall with one DCB compared to the other. If the drug persists without producing toxic effects, this can translate to the patient's outcome—the patient may do better because the drug will be there for a longer time. For instance, we know that the solid phase for IN.PACT Admiral DCB is greater than for the Lutonix DCB, and it remains in the arterial wall for a longer duration; thus, the drug is delivered for a longer time. However, head-to-head comparisons must be performed, both in terms of preclinical and clinical evaluation, to gain further knowledge.

Dr. Granada: It is important to highlight the profound differences between an animal's normal healthy artery and a human's atherosclerotic vascular environment. One has to be careful about extrapolating experimental findings into clinical lessons; however, we have learned that biological signals from experimental studies have translated into clinically measurable findings. For example, the pharmacokinetic behavior of DCBs is a good biological surrogate for clinical efficacy. Also, in the drug-eluting stent era, we learned that negative biological signals at the tissue level correlated with adverse clinical events in humans. Although one has to be careful about translating these findings between an animal and a human, we have learned to identify the signals that could potentially produce negative clinical events in humans.

SAFETY AND EFFICACY OF DCBs

What has your preclinical experience shown in terms of efficacy?

Dr. Granada: Pharmacokinetic studies have been the cornerstone of efficacy or the most important surrogate for efficacy. We have learned that maintaining stable, predictable tissue levels over time correlates with clinical efficacy in humans. Also, tissue efficacy studies evaluate the effect of paclitaxel on the vessel wall, as measured by the amount of fibrin that is accumulated and the amount of smooth muscle cells that are inhibited or killed by the drug over time. Tissue levels have been shown to correlate with the healing process over time and can be used as a surrogate of safety and efficacy in humans.

Dr. Virmani: I would say that the IN.PACT Admiral DCB has better efficacy as compared to Lutonix if you look at the depth of distribution of the drug or effects on the arterial wall. If you look at the circumference, there is better distribution. With IN.PACT Admiral DCB, there is 78.9% patency at 2 years, which is very high—higher than I would have expected. I think IN.PACT Admiral DCB is a very good system, and the clinical data speak for themselves.

What has your preclinical experience demonstrated in terms of safety?

Dr. Virmani: In terms of the preclinical work I did for IN.PACT Admiral DCB, I did not see much distal emboli,

even at three times the dose. In the preclinical work I have done for Lutonix, I did not see distal emboli when three balloons were deployed at the same site; however, I was blinded to how the balloon was delivered.

Dr. Granada: One of the important lessons about safety is to maintain therapeutic tissue levels over time that do not go beyond the boundaries of potential toxic effects. The biological effect of drug can be clearly identified and quantified through standard histologic methods.

What key parameters are most important for evaluation?

Dr. Virmani: For me, the most important parameter is delayed healing—specifically persistence of fibrin, fewer smooth muscle cells, and level of endothelialization. If healing is not complete, the area is not fully covered by smooth muscle cells, proteoglycan, and collagen. Instead, we still see persistence of fibrin, fewer smooth muscle cells, and more proteoglycan, which I call delayed healing. That tells me that the drug is effective.

Dr. Granada: A very important parameter that is being shown by Dr. Virmani's lab is the potential of paclitaxel to inhibit and kill smooth muscle cells in the media in the vessel wall. Most importantly, quantification of this effect throughout the entire vessel wall can define the biological effect of paclitaxel in smooth muscle cell proliferation and vessel healing. When you combine these parameters, you can essentially create a reproducible picture of the safety profile of DCB technologies.

Do you have any safety concerns regarding DCBs as a class? Regarding IN.PACT Admiral in general?

Dr. Virmani: For a one-time dose, no, I don't think there are safety concerns with either DCB.

Dr. Granada: I think the most important thing is to go back to the clinical data. If you look at group class effect, DCBs in the superficial femoral artery (SFA) have not really shown any safety concerns. I think it is fair to say that DCBs are safe for that particular application. At the present time, we have not seen evidence of arterial thrombosis or aneurysm formation in the SFA after DCB treatment despite the wide use of the technology. In the territory below the knee, it is still an open question because it is a very difficult territory to treat—there is a lot of plaque burden, and there is the potential for embolization into a territory that has very poor vascular runoff. I think it is fair to say that the overall safety for DCBs below the knee is still under investigation.

THE SCIENCE BEHIND CLINICAL PERFORMANCE

Pivotal trial evidence proves the safety and efficacy of DCB therapy through 2 years; however, there is variability in efficacy across the technologies. What makes a DCB effective, and what mechanism of action is critical to success?

Dr. Granada: As previously discussed, the pharmacokinetic profile of each DCB depends on the type of coatings developed by the device manufacturer, and it will determine the clinical efficacy of the technology. Specifically for the IN.PACT Admiral DCB, we know that paclitaxel levels in tissue remain within therapeutic levels beyond 28 days. Clinical data show the sustainability of patency rates up to 2 years, but it is challenging to compare results between technologies and trials because the methodologies and the patients enrolled are different. Therefore, head-to-head comparisons between technologies are very difficult to make at the present time. It is fair to say that for DCB technologies, it is remarkable that we can achieve sustainable patency rates up to 2 years with a single drug application, as recently shown.

Dr. Virmani: The duration of time paclitaxel stays in the vessel wall is critical to success. For the IN.PACT Admiral DCB, it is claimed that because of its solid phase, paclitaxel remains in tissue longer, and we have shown that crystals are seen much longer. Both DCBs deliver crystalline paclitaxel. One has larger crystals and the other has smaller crystals, so you could argue that with one, we can see the crystals, and in the other, we cannot see the crystals; however, that does not mean it is not effective. You can argue either way. I think in vitro testing has shown that the solid phase stays around more than 24 hours as far as the IN.PACT Admiral DCB is concerned.

What product differences may play a role in these clinical outcomes?

Dr. Virmani: Solid state makes the difference—how much drug is delivered to the vessel wall and how long it stays there. When delivering a DCB, contact with the vessel wall is important. Pressure can be applied; the longer the pressure, the more drug will be delivered. You could also argue that not only is the pressure important, but it is important how long the balloon is inflated. If the balloon is inflated for 30 seconds versus

180 seconds, it will make a difference. These are all factors that can be tested.

Dr. Granada: I emphasize pharmacokinetics because if you talk about clinical efficacy, you need to make sure that you not only transfer drug but also that tissue levels are maintained over time. The sustainability and reproducibility of the pharmacokinetic profile in each individual patient is extremely important. The second difference is the concept of tissue distribution. If you look at stents, the stents essentially release drug into the tissue in a very uniform and predictable fashion. DCBs essentially maintain tissue levels by adhering crystalline particles on the vessel wall, and those particles release drug into the tissue over time. This distribution is not as organized or predictable as that observed in drug-eluting stents, but it works. The ability to reproduce homogeneous distribution of paclitaxel transfer and sustainability over time is certainly an important concept. The last concept that is important but still poorly understood is the concept of particle dislodgement occurring upon balloon inflation. As part of the process of coating transfer, particles are produced and dislodged off the surface of the balloon and can potentially produce adverse effects, especially in areas with very poor vascular runoff. The development of DCBs that demonstrate lower embolization potential while still achieving reproducible therapeutic tissue levels is warranted.

Based on your preclinical evaluation, which of these technology differences is most critical, and how might it affect clinical outcomes?

Dr. Granada: The most impactful technologic difference that can improve outcomes is the ability to maintain tissue levels that are therapeutic, reproducible, and reliable over time. Finding the right balance between therapeutic effect and safety will be a key technical specification for the development of future-generation DCB technologies.

Dr. Virmani: I would say that the DCB that delivers the most drug is the winner in terms of clinical outcomes. The DCB that has the lowest risk of distal embolization may be important in some patients, but may not be important in other patients, so these factors have to be weighed. ■