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EDITORIAL COMMENT

A Tale of 2 Paclitaxel Stories

Translational Research and the Advancement of Endovascular Combination Devices*

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"In God we trust, all others must bring data."
—W. Edwards Deming (1)

Like almost everything in the history of medicine, the remarkable development of minimally invasive treatment for obstructive arterial atherosclerosis in the last 4 decades has been a perpetually humbling rollercoaster of high hopes, setbacks, and hard-fought victories. The original success of balloon angioplasty was soon tempered by the grave consequences of acute vessel closure. Maintaining acute lumen patency gained after balloon angioplasty was dramatically improved by the introduction of stents; however, this technological breakthrough introduced a new and severe thrombotic risk inherent to the presence of a permanent metallic implant. Optimization of stent implantation techniques coupled with the addition of dual antiplatelet therapy eliminated the need for systemic anticoagulation and vastly reduced the peri- and post-procedural risk of stent thrombosis and myocardial infarction. Since then, use of stents has rapidly expanded into the most complex forms of obstructive coronary disease. It did not take long to realize that this radical safety improvement of stent-aided angioplasty came at a price of perhaps less dramatic yet all too common failure to retain long-term patency due to restenosis. Subsequently, numerous additive therapies were tested to abate in-stent restenosis, from the relatively simple, such as oral medications and plaque modification to the extraordinarily complex and onerous, such as vascular brachytherapy. All of these attempts have failed to make a lasting and universal difference, and again, many have enjoyed an early success only to be eventually doomed by new iatrogenic complications or lack of enduring safety and efficacy. It was not until the development of drug-device combination technologies such as drug-eluting stents (DES) some years later when restenosis rates started to significantly decline. However, even this spectacular milestone was not achieved without paying a higher price: late and very late stent thromboses due to occasional failure to adequately cover stent struts with neointima. Rapid technological improvements as well as maturation of clinical practices surrounding DES use have been able to eventually affirm DES as the standard of care for the interventional treatment of obstructive coronary disease.

The attempt to adapt established DES technologies directly and promptly to peripheral arterial use proved to be more difficult than initially assumed. As a result, the invention of the paclitaxel-coated balloon (PCB) was met with considerable enthusiasm. Ingenious in its simplicity and free of the drawbacks of a permanent implant, the PCB technology consistently demonstrated positive clinical impact on the prevention of peripheral restenosis and became rapidly adopted worldwide. Following several decades of accumulating favorable clinical evidence, the optimism was upended by a massive controversy: increase of all-cause mortality with use of paclitaxel-eluting devices for treatment of

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obstructive peripheral atherosclerosis (2). The finding was initially met with skepticism due to numerous flaws in the original meta-analysis, but it was confirmed throughout multiple subsequent data reviews (3).

The development of PCB was supported by a robust amount of preclinical and clinical data and was accelerated by using a well-characterized drug, including its previous use in coronary stents. However, this entire body of experimental and clinical evidence has not been able to satisfactorily answer questions emerging from the controversy over excessive mortality. The most vexing aspect of this unresolved conundrum is that a plausible mechanistic explanation has not been identified to this day. One of the main reasons is that animal research supporting the technology development has been subordinated to the regulatory process; therefore, its focus is mainly on proving safety. This inevitable necessity is often compounded by hard choices regarding the study design and sample size due to cost, particularly that large animals must be used to approximate clinical relevance. Furthermore, as normal animals used in safety studies are often of limited value in predicting efficacy, the proof of efficacy must often come from early clinical studies. Once the clinical performance milestones are successfully reached, the motivation and resources to continue preclinical investigations subside.

Conceptual and mechanistic studies elucidating the more intricate unknown aspects of cardiovascular technologies are still relatively infrequent, hence very precious. It is therefore commendable that such studies continue to be undertaken by independent researchers to bridge the numerous remaining knowledge gaps. An example of such work is featured in this issue of *JACC: Basic to Translational Science* (4). The study elegantly combines several different and sophisticated research and analytical methods to advance our understanding of paclitaxel's impact on atherosclerosis progression following endovascular intervention at the time of ongoing controversy. Effects of PCB were investigated on experimental plaque inflammation and progression in the rabbits subjected to aortic balloon injury and atherogenic high-cholesterol diet by means of intravascular ultrasonography and Near-InfraRed Fluorescence Optical Coherence Tomography (NIRF-OCT) over 6 weeks. PCBs were found to significantly reduce plaque volume and inflammation assessed by NIRF-OCT and induced outward remodeling in the treated segments in comparison to control and sham animals. The NIRF-OCT in vivo evidence of inflammation suppression was corroborated by histopathologic evidence of fewer macrophages and by the finding of reduced RNA expression of cathepsins by paclitaxel in a dose-dependent manner in human vascular smooth muscle cells. This study is particularly important as it presents the potential in vivo biological mechanisms of action of paclitaxel in atherosclerotic tissue.

Several limitations of the study must be pointed out, however. Legitimate questions surround the adequacy of the atherogenic diet-fed rabbit model in simulating processes underlying human atherosclerosis and its reaction to endovascular intervention. This model can be rightly criticized as a fairly remote surrogate of human atherosclerosis because it is exogenically induced and devoid of any innate pathological mechanism of atherosclerosis. Consequently, it is prudent to not overinterpret any outcomes obtained in this model as being representative of the human scenario. In all fairness, however, such caution is universally advisable in regard to any animal surrogates of human anatomy and physiology. Furthermore, the observation period following the therapeutic intervention in this study was very short, and the magnitude of effects observed was relatively modest, but it is mostly through such painstaking, deliberate, small steps rather than monumental "Eureka!" moments, that our knowledge typically progresses. Thus, the present study should be appreciated as a valuable mechanistic piece of the paclitaxel puzzle. Even though the multimodality finding of decreased inflammation following local paclitaxel application to a diseased and injured rabbit artery may seem completely unrelated to the controversy of paclitaxel mortality, without it (and many more), we can be certain to not get any closer to an answer. The present study, in addition to its cardinal findings advancing interventional pathobiology of paclitaxel, is an important reminder of the imperative to continue independent translational research as an indispensable component of cardiovascular technology development and validation.

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