After the Meta-Analysis…


It has been almost a year since a meta-analysis linking paclitaxel use in peripheral artery disease (PAD) applications was published, immediately turning a relatively stable medical field upside down. Through numerous trials and across myriad devices, paclitaxel delivery had an established role in most clinical algorithms, with long-term level 1 data earning it the status of "gold standard" in many practices. That a widely used therapy for lower extremity PAD might carry an increased mortality risk was unthinkable.

Long-held maxims and preconceived notions were challenged. Methods were questioned and conclusions debated, and a host of possible explanations emerged. But, no one had any idea what would happen as the signal was explored.

A silver lining in the saga has also emerged: In a remarkably short time, the collective understanding of our clinical trials has unquestionably been enhanced as numerous groups comprising countless individuals have devoted their research hours (and what was left of their free time) to exploring the signal.

We have learned more about PAD clinical trial design and conduct in the past 10 months than in the previous 10 years. We now understand the critical importance of obtaining long-term follow-up in all study patients. We've begun to better recognize confounding influences in both study arms, with particular focus on control arms, as well as the potential effects of what historically have been poorly understood biases. And, new levels of understanding around the science of drug doses have emerged.

Perhaps most importantly, we are learning what a community can do when it works together toward a common goal, exploring what's best for its patients. Regulators have requested more data from long-approved devices, and natural competitors have collaborated in unprecedented ways (while still competing, of course). In retrospect, the amount of data that has been collected, collated, analyzed, presented, and published over this short period is nothing short of amazing.

However, after all that effort, there is still no certainty as to whether there is a causal link between paclitaxel and mortality in PAD patients. This continues to leave physicians, trialists, administrators, and regulators in an uncertain and morally challenging position.

In this edition of *Endovascular Today*, we explore what we've learned since the meta-analysis was published and how experts are approaching the challenge of uncertainty in past, present, and future applications of paclitaxel.

We begin with a discussion with Konstantinos Katsanos, MD, lead author of the meta-analysis, who shares what he's learned since its publication and his thoughts on the vascular community's response.

Next, Prof. Varcoe joins an expert panel of key trialists, including Marianne Brodmann, MD; William Gray, MD; Peter A. Schneider, MD; and Thomas Zeller, MD, PhD, to discuss considerations in future trial design, adjudication, and paths forward. An interview with representatives from the FDA Center for Devices and Radiological Health follows and provides insight into the August 2019 letter to health care providers, lessons learned for future trials and follow-up protocols, and additional plans for outcome monitoring.

Paclitaxel products remain on the market in most locations, although opinions on when to use them varies. The FDA suggests use in patients at high risk for restenosis; however, this population is not concretely defined. We've asked a panel of experts including Andrew Holden, MBChB; John H. Rundback, MD; Koen Deloose, MD; Gary M. Ansel, MD; Herbert D. Aronow, MD; Prof. Brodmann; and Dr. Schneider how they are addressing this challenge in their practices.

Next, Prof. Holden discusses the dose-response effect and the impact of improved patient-level data collection. Addressing newer data collection capabilities, Anna Krawisz, MD; Eric A. Secemsky, MD; Robert Yeh, MD; Daniel Bertges, MD; and William Schuyler Jones, MD, explain the relevance of real-world data to the safety discussion and summarize several projects investigating the mortality signal utilizing real-world data analyses.

Amit N. Keswani, MD, and Joshua A. Beckman, MD, consider the natural history of intermittent claudication, exploring the presentation of symptomatic PAD and the associated major adverse events, which begs the question: What effect might paclitaxel have in these patients?

Finding a potential mortality signal from paclitaxel-coated devices in the peripheral arteries was surprising given the experience with paclitaxel in the coronary arteries. Therefore, Mark K. Tuttle, MD, and Jeffrey J. Popma, MD, take a retrospective look at paclitaxel in the coronary arteries, reviewing the safety and efficacy profile of a therapy ultimately supplanted and not without its own concerns about late effects—but with no toxicity link.

Shifting away from the paclitaxel discussion, Dr. Deloose sheds light on lesion-specific SFA device selection, while Dr. Steiner and Andrej Schmidt, MD, look at recent advances in next-generation SFA technologies.

Concluding the issue, we interview Patrick Chong, MBBS, about the BASIL-3 trial, NICE abdominal aortic aneurysm guidance, and his advice for engaging in online clinical discussion platforms.

Although comprehensively addressing every question raised by the paclitaxel signal remains elusive, we hope this special edition helps to shed light on the current challenges facing practitioners, the explorative efforts already underway, and the next steps as we move toward establishing the safety, or otherwise, of this effective antiproliferative tool. ■

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