Renu Virmani

Arterial wall response to drug-coated balloons

Drug-coated balloons are a relatively new endovascular tool for the treatment of patients with peripheral arterial disease. Coated with an antiproliferative drug, these balloons limit cellular growth and prevent restenosis, which is a serious complication associated with the procedure. *Confluence* spoke with Dr Renu Virmani, President of the CVPath Institute, Gaithersburg, Maryland, US, who presented pre-clinical data on the IN.PACT® Admiral® drug-coated balloon at the 2016 Charing Cross Symposium in London. Data demonstrated that IN.PACT® Admiral® sustained paclitaxel levels in tissue over time, facilitating an extended retention of the drug in tissues, which is thought to prolong anti-restenotic effects.

What is peripheral arterial disease, and what are the main therapeutic approaches for treating the condition?

Renu Virmani (RV): Peripheral arterial disease (PAD) is a condition that has been neglected for many years. Patients usually present with claudication, which involves pain or difficulty walking. The majority of the time, this is secondary to atherosclerosis and also medial calcification, which is unique to the peripheral arteries, appearing above the knee in the majority of cases for claudicants, and below the knee for those with chronic limb ischaemia.

Before drug-coated balloons (DCB) were introduced, there were two percutaneous means of treating claudication in patients with PAD; one was balloon angioplasty and the other was stenting with bare-metal, self-expanding stents. Additionally, there was the option of surgery, which is now more prevalent in patients with a higher degree of chronic limb ischaemia and a Rutherford Score of 5 or 6.

What is the drug of choice used in DCBs and why?

RV: The majority of DCBs utilise paclitaxel, which has to be administered in a matter of minutes to the target vessel. The balloon can be coated with a fairly high dose of paclitaxel, up to 3.5 µg/mm^2, as seen with Medtronic's IN.PACT® Admiral®. The lowest dose used is 2 µg/mm^2, as seen in the Lutonix® 035 DCB.[1]

Paclitaxel is extremely effective. The drug works on the smooth muscle cells and endothelial cells of the vessel wall, which are found beside inflammatory cells. Most DCBs use a crystalline form of paclitaxel; if the drug were more amorphous, it would dissolve and be immediately washed away. Its cytotoxicity interferes with the beta-tubulin of microtubules in order to prevent the target cells from multiplying. The idea is that both the number of cells proliferating and the total number of cells that are able to proliferate will be reduced, resulting in a lower build up of new plaques. At 1 year, successful treatment with DCBs results in 80–90% of patients being free of symptoms, compared to only 50–60% when non coated, plain balloons are used.[2]

How do different DCBs compare?

RV: The unique aspect between different types of DCBs is the excipient used. For Medtronic's IN.PACT® Admiral®, the excipient used is urea, and in the case of the Lutonix® 035 DCB, sorbitol and polysorbate are used. Other DCBs make use of iopromide, for example, which was actually one of the first excipients ever tried. The IN.PACT® Admiral® DCB also uses the higher paclitaxel dose of 3.5 µg/mm^2 and is unique in the sense that it has a solid phase of paclitaxel with high crystallinity. This crystallinity allows the drug to stick to the arterial wall for a longer time, adhering for as long as 90–180 days. IN.PACT® Admiral® also delivers a high volume of paclitaxel to the arterial wall when first administered – as much as 50 ng/mg of arterial

tissue. This figure falls quickly, but is maintained at relatively high levels, with around 5–10 ng/mg tissue remaining after 30 days or so.

What factors affect the performance of DCBs?

RV: The method of administration of DCBs is important. One important characteristic is the balloon-to-artery ratio. Normally, a balloon-to-artery ratio of one is used for non-coated balloons, as physicians want to avoid injuring the artery. However, in the case of DCBs, the importance lies in how the drug is released, how well it adheres, and the impact it has on the vessel wall to aid drug transfer. The excipient used is also a key influential factor in the success of drug delivery and sustaining drug levels in tissues. The excipient keeps the drug on the surface of the vessel, allowing slower absorption and improved binding to the arterial wall (Figure 1).

Studies by Bard have shown that where the balloon-to-artery ratio was less than one, the balloon was less effective at preventing target lesion relapse; where the ratios were greater than one at the time of balloon deployment, the results yielded a much lower percentage of target vessel revascularisation.[3] Therefore, in this case, if the balloon-to-artery ratio is a little greater, you have better results. Additionally, it has been shown that if the balloon is inflated for a longer period of time, say 3–5 minutes instead of 60 seconds, there is improvement in angioplasty results, possibly due to mechanical effects.[4]

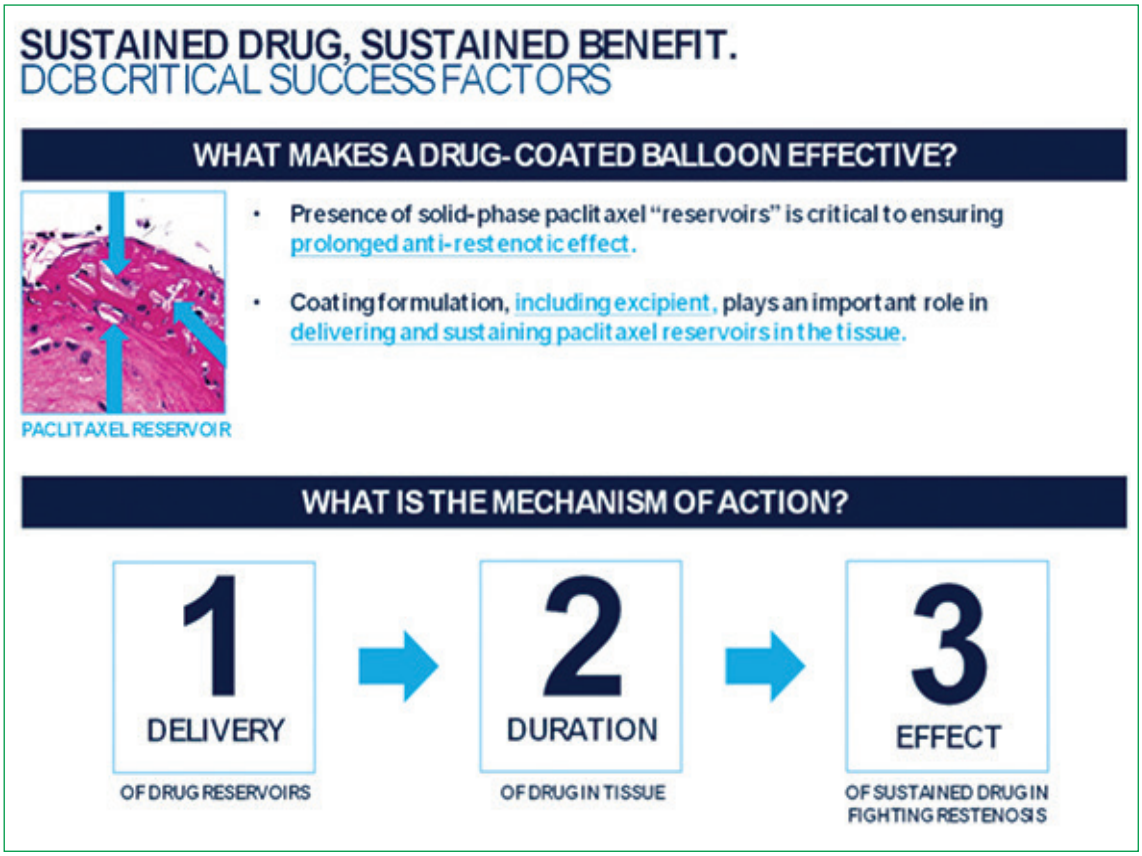
The experience of the physician is also a strong influential factor; those who have been exposed to many cases, who have done the procedures for a long time and know the nuances and differences between DCBs are far more successful. The amount of drug used may also make a difference. I do not believe that if you apply less drug, you see less effectiveness, but this principle may apply.

Are there any limitations associated with DCBs?

RV: The main limitations are with administration. The drug is delivered only once and you have to ensure that it lasts for a long time. Over time, the effect of drug will decrease, and if you look year to year, target vessel revascularisation will increase. So far, a 5–10% loss in the effectiveness of the balloon over 1 year and into the second year is expected.[5] I expect the same thing will be observed at 3 years.

fig. 1

Critical success factors of DCBs and mechanism of action



The problem is that not all of the drug loaded onto the balloon can be used. A fair amount is lost during delivery of the balloon to the target site; more is lost to circulation when the balloon is expanded and some also disappears into the distal bed. Where the same balloon is used in multiple places you will also get less drug on the vessel. We need better efficiency and uniform coating of the drug to improve binding to the arterial wall. Other companies are striving to increase binding efficiency, but IN.PACT® Admiral® and Lutonix® 035 are currently considered some of the most effective DCBs. Conversely, too much exposure to paclitaxel can also cause problems. The total drug dose and, therefore, the total number of balloons one patient can receive are important considerations. Although high levels of the drug are only sustained for a short period of time, complications still occur; it is thought that there may be an increased risk of aneurysms if too much injury is caused and too much drug delivered.[6,7] Distal embolisms, which can impact the healing of ulcers, can occur in those with chronic limb ischaemia; patients can develop gangrene and, in more extreme cases, may also require amputations.[8] However, on the whole, we have generally seen very few complications with DCBs. The success of the balloon has been very dramatic and if I had PAD, I would want the DCB.

How does the efficacy of DCBs vary in different cohorts of patients with PAD?

RV: There is a great deal of variability observed in patients with PAD. In terms of severity, those with chronic limb ischaemia will have a worse outcome compared to patients with an early Rutherford score of 2, 3 or 4. Overall, the disease is more common in diabetic patients and smokers. Patients with diabetes present with a more diffuse form of the disease, with increased severity and calcification, and can also be affected by diabetic neuropathy, where claudication may not be present but difficulty in walking still occurs. Such patients tend to have a poorer outcome when compared to non-diabetics, due to the extent of their disease. Despite their disease severity, the two-year gender and diabetic subgroup analyses from the IN.PACT Superficial Femoral Arterial Disease (SFA) study showed a dramatically improved outcome associated with the use of DCBs for restenosis diabetic patients, compared with the use of non-coated balloons.[9]

There is also variability observed between patients in regard to lesion length, which in itself can have a large impact on outcomes. Patients with shorter lesions can expect better outcomes and are generally able to avoid target vessel revascularisation. The extent to which peripheral arteries are calcified also makes a difference, as well as whether it is an atherosclerotic calcification or a medial Monckeberg's calcification. Higher calcification of arteries reduces the efficiency of drug delivery. If you have a stone and you apply powder on top, will that powder stick to the stone? Of course not. We need to be able to crack that stone – the calcified lesion – in order to allow drug penetration.

What was the aim of the IN.PACT SFA clinical trial programme?

RV: Phase I of the IN.PACT SFA study was initiated in 2010 and evaluated the efficacy of IN.PACT® Admiral® for treating claudication or ischemic rest pain in patients with SFA disease and proximal popliteal artery lesions. Physicians had to first optimise results by mapping these artery lesions and also perform a balloon dilatation to prevent the use of a stent, ensuring no prolapse and that positive results on the angiogram (stenosis <50%) were achieved. Following this, patients were randomised to receive treatment with either IN.PACT® Admiral® or a non-coated balloon in a 2:1 ratio.

Over 300 patients were involved, with assessment after 1, 6 and 12 months, and every year after that for up to 5 years. At 12 months, Doppler echocardiographs were used to evaluate patient outcomes, which were measured in terms of primary patency: the rate of flow through the graft and artery (peak systolic velocity ratio <2.4).

Randomisation has been strongly upheld to prevent bias. The primary efficacy was adjudicated by the blind Clinical Events Committee for clinically driven target vessel revascularisation, or by core laboratory. This is the first time that such a powerful study has been done in this area and it really is a true, blind study.

What results have the IN.PACT studies shown so far?

RV: The first results were released after 1 year and have been very encouraging.[2] At 12 months, the primary patency was 82.2% in patients treated with IN.PACT® Admiral®, compared to 52.4% in patients

using a non coated balloon, which is an amazing difference. For the second year, patency for DCBs fell slightly to 78.9%, which is still a very good result overall. In comparison, patency observed in the Lutonix® 035 DCB at 1 and 2 years is around 62.5% and 58.6%.[4,10]

These data mean that re-intervention rates for patients administered the IN.PACT® balloon are low – if the patency is as high as 82%, there is no need for clinically driven revascularisation in 97.6% of patients. An important question to ask is: does the patient have to have another procedure? Target lesion revascularisation for patients treated with IN.PACT® Admiral® is as low as 9% at year 2, whereas in the case of Lutonix® 035, this value is as high as 18%.[5,11]

Overall, I think that the IN.PACT study has shown some of the best results for illustrating the dramatic differences between DCBs and non-coated balloons. Results show that drug delivery, the solid phase of paclitaxel and the balloon itself are important, but ultimately, what matters most is the effects seen in the patient population. There is a real correlation between clinical outcomes and the design and performance of different DCBs. Not all balloons are created equal.

How can pre-clinical studies influence patient outcomes?

RV: Success is measured clinically, in patients, but animal studies are important. Preclinical studies, most commonly performed using swine models, help to answer some initial research questions: do we see more drug uptake? Do we see drugs staying in the arterial wall for longer? Do we see more crystalline material – and if there is more crystallinity, is the paclitaxel bound to last longer? These questions should be asked before deciding what technology to use in patients.

In the case of IN.PACT®, animal studies have shown that, at 90 days, the smooth muscle cell loss, both in depth and circumference, appears to be much better when compared to Lutonix® 035. We believe that this is to do with that fact that IN.PACT® Admiral® carries the drug in a solid state for a longer period of time than Lutonix® 035. This creates paclitaxel 'reservoirs' in tissues, which have a more long-term effect (Figure 2).

I have seen DCBs that, after showing very little effect in animals, also fail in human studies. For me, it is very important to be able to see the biological effects at 30 days and 90 days in normal animals, for

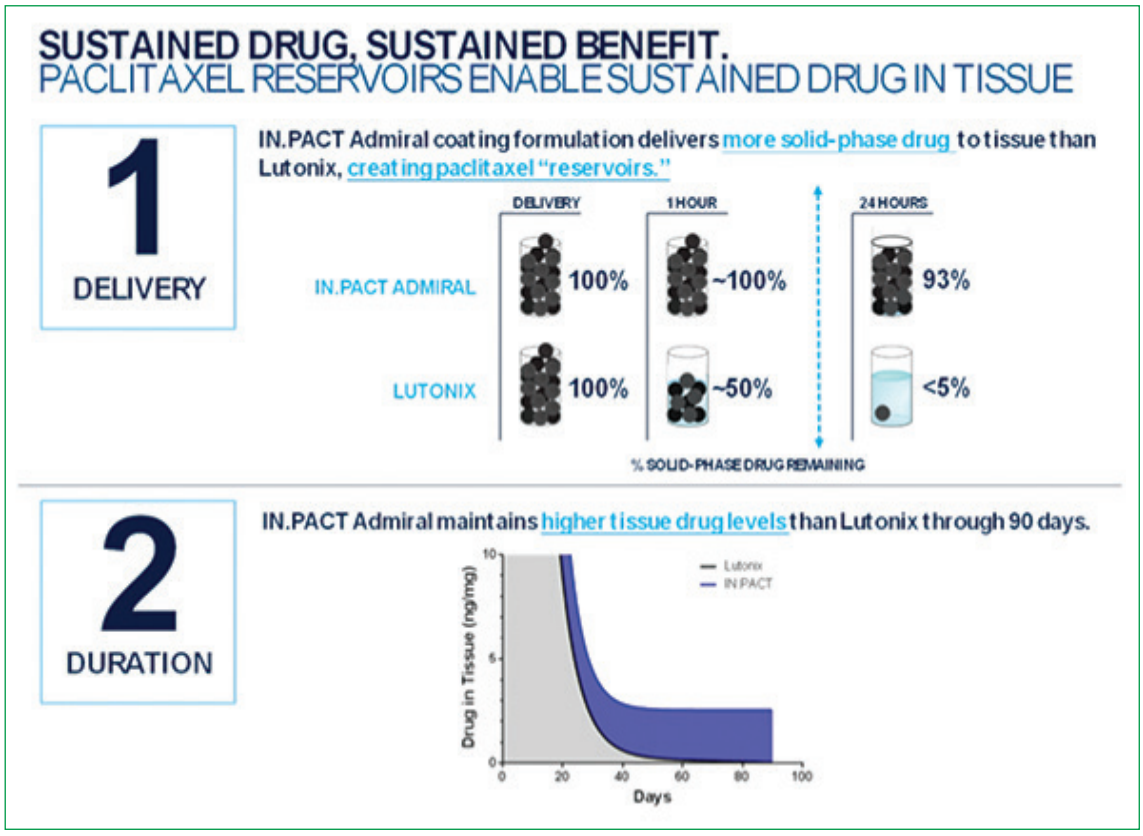


fig. 2

Comparison of drug delivery and duration of IN.PACT® Admiral® vs Lutonix® 035

example, by quantifying the distal emboli that may occur, or the amount of drug that is retained in the vessel. All of these things help us to predict how good the balloons are. By looking at pre-clinical results, one can conclude which balloons will be better than others in a clinical setting.

What are the next steps for DCBs?

RV: Now that we have seen so many dramatic differences between coated and non-coated balloons, the FDA is encouraging companies to randomise their studies. The next study data will most likely be randomised against IN.PACT® Admiral®, or perhaps Lutonix® 035 – this head-to-head comparison of two DCBs will the first of its kind.

With more DCBs being approved, the main question will be around how to distinguish one balloon from another. It's all about efficacy. Ultimately, if data for a new DCB are better than IN.PACT® Admiral®, it will have some say in the market; if not, questions will be raised about whether the new balloon should be used. Just because a balloon is new, that doesn't necessarily mean that it is better.

How do you expect the treatment of conditions such as PAD and SFA to change in the future?

RV: In general, the first line of treatment should always be DCBs. I would prefer to only see stents used if DCBs fail. There are, however, cases where physicians have no choice but to stent, such as if the patient has a dissection or plaque prolapse. Additionally, DCBs do not work as effectively for long lesions.

DCBs have been well received by both physicians and patients, and the results have been very good. I think that in the future there will be a huge amount of competition between DCBs, even in the US. There are 10 or 12 DCBs approved Europe, with only two approved in the US – this is likely to increase to three this year, and perhaps four the following year, but it will take time. Currently, around 30–40% of PAD patients require stents due to failure of PTA. Good results have been shown for the Zilver PTX™ stent from Cook Medical at 5 years, which will likely increase the use of stenting, especially for long lesions and highly calcified lesions.[12] There will be a place for both technologies and this will be for the good of the patient.

Patients are the benefactors of these advances. Overall, the treatment of patients with PAD will be much better tomorrow than it is today. Despite the excellent advances over recent years, there is still room for improvement and I think that these devices will help us greatly improve patient care.

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