A Novel Device to Prevent Neointimal Hyperplasia Restenosis: The DANCE and LIMBO Trials

Interview by Jen Ford

Dr George Adams is the principal investigator of the United States arm of the multinational LIMBO trial. This study examines below-the-knee intervention with the novel Bullfrog balloon catheter (Mercator), which provides direct drug delivery to the adventitia to prevent neointimal hyperplasia restenosis. He spoke at the 43rd Annual VEITH Symposium on the initial results of the LIMBO and DANCE studies.

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VDM: You're here to talk about the DANCE and LIMBO studies. Could you give us a little background on them?

Adams: DANCE is an above-the-knee study and LIMBO is a below-the-knee study. The Achilles' heel of peripheral arterial disease treatment has been restenosis. These two trials address this problem with a novel approach where we use the Bullfrog device to directly deliver an injectable drug to the adventitia to prevent neointimal hyperplasia and tissue scarring associated with restenosis. There are two interesting points about this Micro-Infusion method. First, the drug is delivered via a micro-needle that is sheathed by the same balloon that deploys it. When you inflate the balloon, the 34 g micro-needle passes through the vessel wall and into the adventitia, and because we mix contrast with the drug we can readily visualize the drug getting to the targeted region to prevent smooth muscle cell proliferation. Second, since restenosis arises due to the vascular inflammatory reaction inherent after intervention, we use an anti-inflammatory steroid, dexamethasone, rather than an anti-neoproliferative to quell the restenotic consequences and extend the durability of the intervention.

VDM: What have you found remarkable about the results so far?

Adams: Well, the results have been very interesting. They appear to indicate that the Micro-Infusion of a steroid to the perivascular tissue during intervention is not inferior, at least in the femoropopliteal application (DANCE), to the 1-year Kaplan-Meier estimate of primary patency (~80%) and the point estimate (~mid-70% range) of the anti-proliferative (paclitaxel) drug-coated balloons. Another nice thing is that you know exactly where the drug is going. You get 100% penetration of the drug because you can visualize its delivery under x-ray and confirm that you have bathed the vessel in therapeutic agent.

VDM: Were there any results that were particularly surprising to you?

Adams: In terms of surprise, looking at the patient demographics we treated a higher proportion of Rutherford 4 patients and African-American patients, more severely calcified lesions, more popliteal lesions, and a greater percentage of more complex TASCII B-D lesions than were treated in the femoropopliteal drug-coated balloon studies. Each of these risk factors typically yields worse outcomes in these studies. Yet, the primary patency was 80% out to 390 days by Kaplan-Meier estimates, which again is very similar to the drug-coated balloon outcomes but in a group of patients with more complex lesions and more challenging PAD. The other exciting thing is to think about the future and personalizing therapy. With this, we could choose certain treatment strategies based on the patient, and make our strategy more personalized. For example, treatments may differ for a diabetic versus a non-diabetic, or a man versus a woman, or an African-American versus a Caucasian. It could also differ based on the type of lesion morphology or where the lesion is located. In some of the drug-coated balloon data, you'll note that some subgroups did better than others. For example, males generally responded to the drug-coated balloons better than females, but what we're seeing in DANCE in these same subgroups is that there may be no difference between these treated populations.

VDM: Is there anything different about this device that clinicians should know about?

Adams: Absolutely. The nice thing about this device is that it is a delivery device for almost any drug or biologic. Currently, we are using dexamethasone, but you could use an anti-neoproliferative, you could use stem cells, genes, or various combinations of such. Actually, we are planning and starting trials that will follow the DANCE and LIMBO trials where we will use an anti-neoproliferative. Specifically, in the next study, TANGO, we will administer a sirolimus analog. TANGO will be followed by a study on a combination of the two (an anti-inflammatory and an anti-neoproliferative). In addition to drugs, we'll be able to get to a regenerative medicine stage and the study of stem cells for PAD. We have already received grant support and Mercator is raising capital to pursue these treatment opportunities.

VDM: Can you comment further on the device and offer any tips and tricks?

Adams: As far as the learning curve, and whether there are certain things the operator needs to understand when using this device, the first thing to remember is that you might not be able to penetrate every calcified lesion with the micro-needle, so the operator will need to go above or below these highly calcified segments to deliver the therapy. With each milliliter of injection, the device delivers to an approximately 20 mm-long segment that bathes the adventitia of the vessel, so it is delivering beyond a specific point. Also, the drug contains radio-opaque dye so you can actually visualize the drug delivery and know exactly where it is going. As I mentioned, the drug used in DANCE and LIMBO was dexamethasone, which is an anti-inflammatory.

However, the device is able to deliver almost any drug or biologic. In terms of the device, there are different balloon sizes that allow treatment above or below the knee, so you can get adequate drug therapy to all regions of the leg. The last thing is that this trial includes atherectomy, so prepping the vessel is very important, and we're going to study the effects of atherectomy with the addition of direct adventitial drug therapy. I'm the national co-principal investigator for the United States below-the-knee (LIMBO) study, a randomized, controlled trial of atherectomy with adventitial drug delivery using the Bullfrog device. Dierk Scheinert is the national principal investigator in Europe, where they are investigating balloon angioplasty followed by adventitial drug delivery.

VDM: Is there anything else you want endovascular clinicians to know about this study?

Adams: I think the take-home message is this: First, we know that restenosis is the Achilles' heel of peripheral interventions. Second, personalizing care is very important. We are starting to find out that certain patient populations react differently to the various therapies. Our goal in the future is to develop an algorithm to treat the various patient subsets. You may use one device or drug for a certain subset and a different device or drug for another subset. It's very exciting because the field is advancing, especially with devices that can deliver drug therapy to prevent restenosis. ■