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Adventitial Drug Delivery of Dexamethasone to Improve Primary Patency in the Treatment of Superficial Femoral and Popliteal Artery Disease

12-Month Results From the DANCE Clinical Trial

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ABSTRACT

OBJECTIVES This study was designed to evaluate outcomes of adventitial dexamethasone delivery adjunctive to standard endovascular revascularization in femoropopliteal peripheral artery disease.

BACKGROUND Drug-coated balloons and drug-eluting stents improve patency of endovascular interventions with passive diffusion of antiproliferative drugs. Adventitial dexamethasone delivery targets the initial triggers of the inflammatory reaction to injury, thus potentially providing a potent antirestenotic strategy.

METHODS The single-arm DANCE (Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization) trial enrolled 262 subjects (283 limbs) with symptomatic peripheral artery disease (Rutherford category 2 to 4) receiving percutaneous transluminal angioplasty (PTA) (n = 124) or atherectomy (ATX) (n = 159) in femoropopliteal lesions ≤15 cm in length. A mixture of dexamethasone/contrast medium (80%/20%) was delivered to the adventitia and perivascular tissues surrounding target lesions in all subjects. Thirty-day assessments included major adverse limb events (MALE) and post-operative death. Twelve-month assessments included primary patency, freedom from clinically driven target lesion revascularization (CD-TLR), Rutherford scoring, and walking impairment questionnaire.

RESULTS At 12 months, primary patency rates in DANCE-ATX and -PTA per-protocol populations were 78.4% (74.8% intent-to-treat, [ITT]) and 75.5% (74.3% ITT), respectively. Rates of CD-TLR in DANCE-ATX and -PTA subjects were 10.0% (13.1% ITT) and 11.0% (13.7% ITT), respectively. There were no 30-day MALE + post-operative death events nor 12-month device- or drug-related deaths or MALE.

CONCLUSIONS Direct adventitial delivery of dexamethasone appears to be an effective and safe therapy to prevent restenosis. Randomized studies are needed to further test this possibility. (Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization [DANCE]; NCT01983449) (J Am Coll Cardiol Intv 2018;■:■–■)

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

ADD = adventitial drug delivery

ATX = atherectomy

CD-TLR = clinically driven target lesion revascularization

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

DEX = dexamethasone

ITT = intent-to-treat

K-M = Kaplan-Meier

MALE = major adverse limb event

POD = post-operative death

PP = per protocol

PTA = percutaneous transluminal angioplasty

TBI = toe-brachial index

Relatively poor patency has been a limitation of percutaneous transluminal angioplasty (PTA), atherectomy (ATX) and bare-metal stents in patients with peripheral artery disease. To that end, reducing mechanically induced inflammatory injury to the vessel wall and suppression of neointimal hyperplasia with local drug delivery have been the foci of research to improve outcomes (1-3). The cytotoxic antiproliferative agent paclitaxel has been delivered via drug-coated balloons (DCB) and drug-eluting stents (DES) with superior patency rates when compared with uncoated PTA alone (4-6). The addition of new drug delivery tools and techniques to the peripheral interventional armamentarium appears necessary to further reduce restenosis rates.

Vascular inflammation has been strongly linked to the development of atherosclerosis (7,8) and restenosis (9), particularly in peripheral arteries. The adventitia and perivascular tissues surrounding the artery play a major role in the regulation of inflammation, cell recruitment, and cell proliferation after vascular injury (10,11), thus these tissues have become a target for managing inflammation and preventing restenosis after endovascular intervention. The corticosteroid dexamethasone has a potent anti-inflammatory action and reduces the signal cascade that leads to hyperproliferative responses. Thus, it is considered for its potential ability to reduce the signals that lead to restenosis without the cytotoxicity associated with paclitaxel.

Adventitial and perivascular drug delivery through microneedle infusion catheters is proposed as an alternative to DCB and drug-eluting stents. The principal benefit of this approach is that the therapy may be tailored to the patient and the pathogenesis of the disease, because microneedle injection of liquid therapeutic agents is not limited to agents that can be coated onto balloons or stents.

Evidence of clinical benefit by targeting vascular inflammation with adventitial and perivascular drug delivery in a robust clinical evaluation has not previously been available. A single-center pilot study of adventitial dexamethasone delivery using the Bullfrog Micro-Infusion Device (Mercator MedSystems, Emeryville, California) in 20 subjects reported an 81% primary patency rate at 1-year follow-up (12). The DANCE (Dexamethasone to the Adventitia to Enhance Clinical Efficacy After Femoropopliteal Revascularization) trial was subsequently initiated to assess the safety and efficacy of the adventitial delivery of dexamethasone in a larger group of patients with symptomatic femoropopliteal artery disease.

METHODS

STUDY DESIGN. The DANCE trial is a prospective, multicenter, single-arm, open-label study investigating the safety and effectiveness of adventitial drug delivery of dexamethasone (ADD-DEX) to reduce restenosis after femoropopliteal peripheral artery interventions. The drug was delivered using the Bullfrog Micro-Infusion Device (Mercator MedSystems) (**Figure 1**). The study consisted of 2 pre-specified concurrently enrolling cohorts: DANCE-ATX, in which target lesions were primarily revascularized with any commercially available directional, rotational, orbital or laser atherectomy or debulking device (ATX), and DANCE-PTA, in which target lesions were treated with PTA. Both cohorts allowed for stent placement at the investigators' discretion. There were no differences in the eligibility criteria between the 2 groups. The primary efficacy endpoint, 12-month primary patency, was compared to contemporary published PTA and DCB treatments from pivotal trials of DCB (4,5).

The DANCE trial protocol was approved by institutional review boards at each site, and all patients provided written informed consent before enrollment. The trial was registered on www.clinicaltrials.gov (NCT01983449), and conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and applicable U.S. laws and regulations.

Independent core laboratories analyzed all duplex ultrasonography (VasCore, Boston, Massachusetts) and angiography (Cardiovascular Research Foundation, New York, New York) images. The clinical events committee, consisting of the national principal investigators and an independent medical monitor, reviewed all major adverse events.

DEFINITIONS AND STUDY ENDPOINTS. Infusion success was defined by the visual confirmation of dexamethasone/contrast distribution around the lesion after injection and was graded by the angiographic core laboratory. Revascularization technical failure, defined as >30% residual lumen stenosis, did not disqualify patients from receiving the drug therapy, but was subsequently reviewed by the angiographic core laboratory to determine eligibility for the per protocol population. The per-protocol (PP) analysis excluded: 1) subjects with ≥35% residual stenosis at the end of the case as determined by the angiographic core laboratory, which was 5% higher than