Drug Eluting Technologies

Update On The Value Of The Bullfrog Catheter (From Mercator Medical Systems) To Infuse Dexamethasone Into The Adventitia Of Lesions: Status And Results Of The DANCE Trial And The LIMBO-ATX RCT In Patients With CLTI Due To BTK Lesions

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The Need for Adjunctive Drug Therapy

Targeting different parts of the restenosis cascade with catheter-based drug therapy has become commonplace

Adjunctive Drug Therapy Options

- Direct: Adventitial Delivery with Bullfrog
  - Multi-site drug delivery
  - Needle reaches directly into target tissues
  - Able to visualize placement of drug
  - Few limitations on what drugs can be delivered
  - Capable of polypharmacy solutions or biologic therapy
  - Clinical data in development
- Indirect: Luminal Delivery with DCB
  - Single-site delivery per balloon
  - Drug formulations tailored to diffuse through vessel wall
  - Drug diffusion beyond barriers (e.g. calcification) is difficult
  - Limited to paclitaxel (so far)
  - Extensive, positive clinical data (above the knee)

The Bullfrog® Micro-Infusion Device

"Painting" the vessel with 0.5 mL per cm of lesion:

Clinical Trials of Adventitial/Perivascular (Interstitial) Therapy with Bullfrog Delivery

- Vomapanitase
- Dexamethasone
- Temsirolimus
- PRO201-115
- PR201-115 Dose-escalation RCT
- Enrolment: 2018
- Course: 2019
- TANGO
- LIMBO-ATX
- LIMBO-JTA
- TWIST
- Enrolment: 2018

Disclosures
12-Month Results from the DANCE Trial

Primary analysis:
DANCE-ATX and -PTA 12-month patency rates were each superior to historical performance goal (POBA) of 52.5% (P<0.001 for both groups)

Secondary analysis:
DANCE-ATX and -PTA 12-month patency rates were each non-inferior to the contemporary performance goal (LEVANT-2 & In.PACT-SFA) of 72.3% (P<0.001 for ATX and P<0.004 for PTA)

2-Year DANCE Result: Upstream Targeting of Inflammation Produces a Resilient Effect

DANCE-ATX DANCE-PTA
Month: 6 12 18 24 Month: 6 12 18 24
Patency: 96.0% 84.2% 76.6% 72.2% Patency: 94.1% 77.3% 70.1% 68.9%

How Did We Go from DANCE to LIMBO?

• 2-year DANCE data for both Atherectomy (N=259) and PTA (N=124) groups included the following subgroup characteristics:
  - Diabetes Mellitus 50.3% 52.4%
  - Severe Calcification 29.7% 21.3%
  - Popliteal Involvement 16.4% 18.5%

• How will these results translate into below-the-knee therapy?

TVAL as a Primary Endpoint in BTK Studies

• Safety:
  - Freedom from major adverse limb event (MALE) and post-operative death (POD) at 30 days post procedure

• Efficacy:
  - Transverse-view vessel area loss percentage (TVAL) of the target lesion at 6 months (or prior, in the case of any TLR) by core lab quantitative vascular angiography

LIMBO Study Design

• Two concurrent trials (LIMBO-ATX [U.S. - ENROLLED] and LIMBO-PTA [EU])
• Each trial includes up to 100 Rutherford 4/5 and 20 Rutherford 6 subjects with BTK lesions up to 25-30 cm, randomized 1:1
  - Control: Subjects receive revascularization (ATX or PTA based on study)
  - Treatment: Subjects receive revascularization and then Bullfrog delivery of dexamethasone at dose of 0.8 mg/cm of lesion
• Primary Endpoint: 6 month angiographic TVAL (transverse-view vessel area loss)

TANGO: Applying a -limus Drug in BTK

BTK success have mainly been -limus eluting stents in focal lesions

Adventitial tenofovir delivery produces similar PK profile to DES
Leading the Way into TWIST

Restenosis results from the inflammatory cascade:

- Inflammation
- Neointima formation
- Hyperplasia/narrowing

Upstream targeting of the early inflammatory process limits or eliminates downstream restenosis, but allows healing and resolution.

Summary and Conclusion

- The ADD-DEX procedure in DANCE has produced positive long-term results in both primary atherectomy (in a challenging patient population) and primary angioplasty intervention that should translate well in below-the-knee lesions.
- The well-known -limus drugs have performed well in coronary drug eluting stents for years, which should translate well to the BTK space.
- Adventitial drug delivery opens the door for a variety of therapeutic applications, including patient specific therapy or polypharmacy approaches.