Adventitial Drug Therapy for Critical Limb Ischemia

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Disclosure

Speaker name: Ehrin J. Armstrong MD

I have the following potential conflicts of interest to report:

☒ Consulting: Abbott Vascular, Boston Scientific, Cardiovascular Systems, Medtronic, Philips

☐ Employment in industry

☐ Stockholder of a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☐ I do not have any potential conflict of interest
Improving Treatment for Critical Limb Ischemia

- While drug delivery has shown improvements in patency rates above the knee, most critical limb ischemia patients are still burdened by recurrent below-the-knee arterial occlusion.
- Drug coated balloons have not been shown to work BTK, and their use in that area is controversial due to drug flaking and downstream distribution of crystalline, cytotoxic drugs.
- Adventitial drug delivery of dexamethasone has demonstrated positive results above the knee, on par with paclitaxel-coated balloons.
- Adventitial drug delivery is not limited by surface area contact, allowing more thorough distribution in smaller, BTK arteries.
Adventitial Drug Delivery (ADD) with the Bullfrog® Micro-Infusion Device

Balloon sheaths microneedle

1.5 mm long Microneedle (34 Ga) penetrates artery for drug delivery

Compliant balloon treats broad range of vessel diameters

Lumen
Media
Adventitia
Penvascular tissue

20% contrast : 80% drug is mixed and co-administered to provide immediate feedback

“Painting” the vessel with 0.5 mL per cm of lesion:
Targeting the Restenosis Cascade

Restenosis results from the inflammatory cascade:

- **Transcription**
- **Endovascular Procedure**
- **Injury**
- **Siyolimus and its analogs** have shown the ability to decrease inflammation and reduce cellular proliferation, targeting multiple aspects of the cascade

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

Sirolimus and its analogs have shown the ability to decrease inflammation and reduce cellular proliferation, targeting multiple aspects of the cascade.
Current Clinical Trials of Adventitial-Perivascular Therapy with Bullfrog Delivery

**Trauma**
- **Vonapanitase**
  - **SFA**
  - **Popliteal**
  - **Infrapop**

**Recoil**
- **Dexamethasone**
  - **DANCE**
    - 283 limbs
    - (159 ATX, 124 PTA)
    - Open-label
    - COMPLETED
  - **LIMBO-ATX**
    - 120 total subjects
    - 1:1 RCT
  - **LIMBO-PTA**
    - 120 total subjects
    - 1:1 RCT

**Signaling**

**Recruitment**

**Proliferation**

**Migration**

**Obstruction**

**Tango**
- 60 total subjects
- Dose-escalation RCT
- (20 control, 20 low, 20 high dose)

Enrollment COMPLETE

Enrolling
Vonapanitase

- Investigational recombinant human chymotrypsin-like elastase family member 1 (CELA1)
- Protease that cleaves peptide bonds in elastin
- Elastin is the major component of elastic fibers that impart elasticity
- No impact on collagen, so vessel strength is maintained
- No arterial aneurysms in preclinical studies or patients in clinical trials
Vonapanitase Phase 1 Endovascular Study

- Randomized, double-blind, placebo-controlled, dose-escalation in patients undergoing PTA of tibial or peroneal artery
- Concentrations 2.5, 5, and 10 mg/mL selected from prior nonclinical studies showing extensive elastin removal
- Cohorts of 8 subjects (2 placebo, 6 active)
- N= 40 subjects
- Enrollment 1 year with 6 mos. of follow-up
- Data available later this year
LIMBO Study Design

• Two concurrent trials (LIMBO-ATX [U.S.] 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)
LIMBO Case Example
LIMBO Case Example
TANGO: Applying a \(-\)limus in BTK

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

Adventitial temsirolimus delivery produces similar PK profile to DES

Comparison of Xience V Everolimus to Bullfrog Temsirolimus Tissue Concentration

<table>
<thead>
<tr>
<th>Days Post-Delivery</th>
<th>Everolimus Stented Area Concentration (Xience V Coronary Stents, 1(\mu)g/mm² dose)</th>
<th>Temsirolimus Injection Site Concentration (Bullfrog delivery of 0.36 mg dose for 6x20 mm segment: equiv dose=0.95(\mu)g/mm²)</th>
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Zakir RM. NCVH 2015.
TANGO Study Design

• Phase 2, dose escalation trial in the U.S.
• Up to 60 Rutherford 3-5 subjects with BTK lesions up to 25 cm, randomized 2:1 during each dose, with Bullfrog delivery after revascularization in every case
  – Control (20 subjects): Saline/20% contrast
  – Low Dose (20 subjects): Torisel® (25 μg/cm of lesion)/20% contrast
  – High Dose (20 subjects): Torisel® (100 μg/cm of lesion)/20% contrast
• Primary Endpoint: 6 month angiographic TVAL (transverse-view vessel area loss)
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

What Is TVAL?

\[
\text{TVAL} = 100\% - \left( \frac{\text{TVA}_{\text{follow-up}}}{\text{TVA}_{\text{baseline}}} \right)
\]

TVA is the shaded area within TL.
Leading the Way into TWIST

• LIMBO and TANGO, along with preclinical research currently underway, provide the foundation for TWIST

• TWIST will be the first polypharmacy trial in the legs

• TWIST will combine antiproliferative drug with anti-inflammatory drug in the attempt to knock out multiple targets in the restenosis cascade
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 polypharmaceutical approaches.
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