Adventitial Drug Therapy Below-the-Knee: Update on LIMBO and TANGO

Ehrin J. Armstrong, MD, FACC
University of Colorado School of Medicine
VA Eastern Colorado Healthcare System
Denver, Colorado, USA
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

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:

- **Hours**: Inflammation
- **Days**: Signal transduction
- **Weeks**: Recruitment
- **Months**: Proliferation
- **HYPERPLASIA/NARROWING**

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

DEXAMETHASONE - LIMUS ANALOGS

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**
  - **Recoil**
  - **Signaling**
  - **Recruitment**
  - **Proliferation**
  - **Migration**
  - **Obstruction**

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

- **Dexamethasone**
  - DANCE
    - 283 limbs
    - (159 ATX, 124 PTA)
    - Open-label
    - COMPLETED

- **Temsirolimus**
  - LIMBO-ATX
    - 120 total subjects
    - 1:1 RCT
    - Enrolling
  - LIMBO-PTA
    - 120 total subjects
    - 1:1 RCT
    - Enrolling

- **PRT201-115**
  - 40 subjects
  - Dose-escalation RCT
  - Enrolling

- **TANGO**
  - 60 total subjects
  - Dose-escalation RCT
  - (20 control, 20 low, 20 high dose)
  - Enrolling
DANCE Preliminary 2-Year Primary Patency
Kaplan-Meier Estimates (per protocol)

DANCE-ATX Primary Patency (PP)

DANCE-PTA Primary Patency (PP)
How Did We Go from DANCE to LIMBO?

- George Adams, MD, presented on Tuesday the 2-year DANCE data for both Atherectomy (N=159) and PTA (N=124) groups, including the following:

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>DANCE-ATX</th>
<th>DANCE-PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>50.3%</td>
<td>52.4%</td>
</tr>
<tr>
<td>Severe Calcification</td>
<td>29.7%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Popliteal Involvement</td>
<td>16.4%</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

- Can the results from these groups inform below-the-knee?
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)
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

Everolimus Stented Area Concentration (Xience V Coronary Stents, 1μg/mm² dose)

Temsirolimus Injection Site Concentration (Bullfrog delivery of 0.36 mg dose for 6x20 mm segment: equiv dose=0.95μg/mm²)

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?

TVA is the shaded area within TL

\[
TVAL = 100\% - \left( \frac{TVA_{f/u}}{TVA_{baseline}} \right)
\]
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.
Acknowledgements to the Study Teams

• DANCE Principal Investigators
  – Mahmood Razavi, MD
  – George Adams, MD

• LIMBO Principal Investigators
  – Dierk Scheinert, MD
  – George Adams, MD
  – Don Jacobs, MD

• TANGO Principal Investigator
  – Ian Cawich, MD