Polypharmacy and the future of PAD and CLI drug therapy

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Employment in industry: No</td>
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<td>Owner of a healthcare company: No</td>
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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:
Current Clinical Trials of Adventitial-Perivascular Therapy with Bullfrog Delivery

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

- **Vonapanitase**
  - **Dose-escalation RCT**
  - **Enrolling**

- **Dexamethasone**
  - **DANCE**
    - 283 limbs
    - Open-label
    - **COMPLETED**

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

- **LIMBO-ATX**
  - 120 total subjects
  - 1:1 RCT
  - **Enrollment COMPLETE**

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

- **TANGO**
  - 60 total subjects
  - Dose-escalation RCT
  - **Enrolling**
Targeting the Restenosis Cascade

Restenosis results from the inflammatory cascade:

- **Hours**
- **Days**
- **Weeks**
- **Months**

**INJURY**

**ENDOVASCULAR PROCEDURE**

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
Polypharmacy enhanced anti-proliferation in vitro

Normalized Inhibition of PDGF-Induced VSMC Proliferation with Various Agents
(PDGF alone=0% inhibition, Actinomycin D alone=100% inhibition)
Preclinical study design

Watanabe hyperlipidemic rabbits → Iliac angiogram
Balloon injury (20-30% over stretch)

1ml perivascular dose: Bullfrog*

Group A: animal 4, vessel 8
Temsirolimus 0.4mg + Dexamethasone 4mg

Group B: animal 4, vessel 7
Temsirolimus 0.4mg alone

Group C: animal 4, vessel 8
Dexamethasone 4mg alone

28-day
Euthanasia,
Blood examination
Histopathologic analysis
E.g. H&E, Movat, BrdU staining

QVA

Pre-Intervention Angiographic vessel diameter

Balloon injury

Micro-Infusion

% over stretch

Serum cholesterol level

Rabbit reference: 30-100mg/dl

Tem; temsirolimus
Dex; dexamethasone
Polypharmacy enhanced anti-restenotic effect

% area stenosis

Relative intimal thickness*

Relative plaque area**

Tem : temsirolimus (0.4mg), Dex : Dexamethasone (4mg)

* Mean intimal thickness/pre-angiographic vessel diameter

** Plaque area/pre-angiographic vessel area

Finn, LINC 2018
Polypharmacy enhanced anti-proliferation effect

Tem + Dex

Tem: temsirolimus (0.4mg)
Dex: Dexamethasone (4mg)

Number of BrdU (+) cell/section

Left upper: BrdU stain (low power)
Right: BrdU stain (high power)
Left bottom: Movat stain

Finn, LINC 2018
Summary

✓ Drug combination therapy (temsirolimus (Tem) + dexamethasone (Dex)) using Bullfrog device significantly reduced balloon injury-induced restenosis compared to Tem and Dex monotherapy in rabbit iliac model.

✓ Following in vitro experimental result, combination therapy using Bullfrog device relatively reduced intimal proliferation compared to Tem and Dex monotherapy in rabbit iliac model.

✓ Bullfrog device and combination therapy may provide a new treatment strategy in lower extremity catheter intervention.
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