PHARMACOLOGICAL TREATMENT OF ARTERIAL RESTENOSIS

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Paclitaxel essentially freezes the microtubules that are in place during cell division. The cells cannot complete cell division and recognizes that something is wrong and destroys itself. This process is called apoptosis or programmed cell death.

Rapamycin works a little differently in that it affects a different pathway that essentially puts the cell to sleep and by doing that it prevents the cell from proliferating. Eventually the Rapamycin is metabolized and the cell wakes up and can operate normally again.
Paclitaxel (Cytotoxic) *Interferes with cell division*

Cytotoxic drugs stabilize microtubules, preventing division in the final stages of the cellular replication cycle and leading to cell death (apoptosis).

Rapamycin/Sirolimus (Cytostatic) *Interferes with cell growth*

Cytostatic drugs hold a cell in G₀ phase, arresting growth but allowing cell to continue functioning.
STUDIES SHOWING CHANGES IN NEOINTIMAL INHIBITION BASED ON VARYING CONCENTRATIONS OF PACLITAXEL

- Dose-dependent response up to 3-4 μg/mm² (effective dose) Less than a ~2.5 μg/mm² dose shows a decreased therapeutic benefit
- Above a 4 μg/mm² dose indicates a limited, incremental efficacy gained

Paclitaxel concentrations following treatment suggest both safety and efficacy

Tissue
- Detectable levels of drug over 180 days in both arms (therapeutic dose and 3x safety margin)
- At 320 days no quantifiable drug is identified in the targeted tissue area (therapeutic dose)

Plasma
- No drug quantified after 48 hours (therapeutic dose)
- No drug quantified after 672 hours (3x safety margin dose)
- Drug concentrations drop 50% within the first 30 min

Porcine ilio-femoral model - Data on file at Medtronic Inc.
An excipient supports the uptake of drug by vessel tissue

- Acts as a molecular spacer to increase paclitaxel surface exposure
- Facilitates paclitaxel transfer through its hydrophilic properties

Tissue Concentration

Blood Concentration

R. Virmani – CIRSE 2012 Oral Presentation
Coating technology provides reliable and uniform drug delivery.

**DESIGN OBJECTIVE:**

**DURABLE / SCALABLE COATING**

Balloon coating in semi-inflated shape:

- Longitudinal Coating Thickness
- Circumferential Coating

~60-70% of dose protected within balloon folds

1 experimental data on file at Medtronic
DCB MECHANISM OF ACTION FACILITATES THE TRANSFER OF DRUG DEEP INTO VESSEL TISSUE

IN.PACT Admiral balloon matrix coating:
- Paclitaxel
- Urea - excipient that controls drug release

DCB inflation:
- Matrix coating contact with the blood
- Urea hydrates causing the release of paclitaxel
- Paclitaxel binds to the wall due to its hydrophobic and lipophilic properties

Paclitaxel penetration:
- Through vessel wall deep into the media and adventitia
- Interferes with the causes of restenosis
- Can remain in the vessel wall for over 180 days at therapeutic levels

1Data on file at Medtronic (GLP Study FS208; GLP Study PS516)
**Provisional stenting rate is dependent on lesion length**

Scaffolds still needed but likely at rates proportional to lesion complexity

Provisional stent rates in DCB trials are a function of lesion length

DEB IS EFFECTIVE IN CALCIFIED LESIONS

- Objective: Assess effect of calcium on IN.PACT DCB efficacy
- 60-patient registry
- SFA de-novo: average Lesion Length 6.1 cm
- Chronic Total Occlusion: 31.7%
- Systematic PTA pre-dilatation followed by IN.PACT DCB

Calcium distribution and severity affect Late Lumen Loss and Primary Patency

Severe calcium may represent a barrier to drug absorption

Calcium distribution evaluation by CTA (circumferential) and DSA (longitudinal)
IN.PACT ADMIRAL IS THE NEW STANDARD FOR PRIMARY PATENCY

Primary patency is defined as freedom from clinically-driven TLR and freedom from restenosis as determined by duplex ultrasound (DUS) Peak Systolic Velocity Ratio (PSVR) ≤ 2.4

(p<0.001 by log-rank test)

*Qualitative Comparison. Not Meant for Head-to-Head Comparison.
1. Clinically-driven TLR defined as any re-intervention due to symptoms or drop of ABI/TBI of >20% or >0.15 compared to post-procedure ABI/TBI
2. Actual event rate by frequency ratio algorithm calculation

*Qualitative Comparison. Not Meant for Head-to-Head Comparison.
**TREATMENT STRATEGY**

1. **PRE-DILATATION**
   - Required for all lesions, prior to DCB procedure
   - Standard PTA 1 mm less than reference vessel diameter (RVD)
   - Balloon length should not be greater than the planned DCB length

2. **ATHERECTOMY**
   - Recommended in severely calcified lesions

3. **DRUG-COATED BALLOON**
   - DCB diameter: RVD = 1:1; length 1 cm beyond lesion on both ends
   - Inflation time ≥ 3 minutes
   - Inflation pressure < RBP as required to reach full DCB expansion

4. **POST-DILATATION**
   - If residual stenosis ≥ 50% or flow limiting dissection
   - Standard or high pressure PTA balloon diameter 1:1 to RVD
   - Short / focal length as necessary to treat the extent of residual stenosis or dissection

5. **PROVISIONAL SPOT STENTING**
   - For persistent residual stenosis ≥ 50% or flow limiting dissections
   - Minimum length as necessary to fully treat the residual stenosis or dissection
Restenosis Summary

**INJURY**
- Stretching
- Denudation
- Recoil
- Leukocyte adherence

**Response Programs**
- Phenotypic switch: quiescent → proliferative and synthetic
- Myofibroblast proliferation
- Progenitor cell differentiation

**Remodeling**
- Negative remodeling
- Fibrosis

**Networks**
- Microvascular networks
- Paracrine factors

**Targets**
- Dexamethasone
Restenosis begins with inflammation, followed by recruitment, proliferation, migration, fibrosis, and hyperplasia. The timeframe for these events is as follows:

- **Hours to Days**: Inflammation, Recruitment
- **Weeks**: Proliferation, Migration
- **Months**: Fibrosis, Hyperplasia

The agents used for treatment include:

- Dexamethasone
- Paclitaxel, -limus compounds
INFLAMMATION IS AT THE ROOT OF RESTENOSIS
OBJECTIVE: To evaluate effectiveness outcomes of adventitial DEX delivered by Bullfrog® Device

Clinical effectiveness evaluation of adventitial DEX after PAD intervention, vs contemporary published data

Prospective, Single Arm, Multicenter Trial

Subject population (n=300), 150 ATX / 150 PTA
Assess safety and feasibility of perivascular dexamethasone delivery following SFA/popliteal artery revascularization

SFA / Pop Lesion -> Successful crossing of lesion & successful revasc. -> Dex Delivery

Bullfrog® Micro-Infusion Catheter injection -> Follow-up (1, 6, 12, 18, 24)
Enrollment complete 12/15/2015

Enrolled Subjects to be followed for 24 Months
THE BULLFROG® MICRO-INFUSION DEVICE
Angioplasty used to open vessel

Bullfrog device inserted to distal target first

After drug delivery to “paint” the vessel, follow up angiogram shows good result
SUCCESSFUL INFUSION

Bullfrog Device with balloon inflated

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Inflated Bullfrog Micro-Infusion Device

After 3 minutes, Full perivascular dispersion >15cm of SFA
BTK Study
US – Kicking off
Q2 2016

LIMBO-ATX

Baseline angiogram and biomarker blood draw

120 ATX (U.S.)

60 controls

60 DEX

24-hour blood draw for Δ biomarkers

1-month blood draw for Δ biomarkers

Clinical, hemodynamic and angiographic follow-up at 6 months

LIMBO-PTA

120 PTA (Germany)

60 controls

60 DEX

BTK Study
Germany/OUS
– Kicking off
January 2016
1. PRE-DILATATION
- Required for all lesions, prior to DCB procedure
- Standard PTA 1 mm less than reference vessel diameter (RVD)
- Balloon length should not be greater than the planned DCB length

2. ATHERECTOMY
- Recommended in severely calcified lesions

3. DRUG-COATED BALLOON vs DIRECT MEDIAL INFUSION

4. PROVISIONAL SPOT STENTING
- For persistent residual stenosis ≥ 50% or flow limiting dissections
- Minimum length as necessary to fully treat the residual stenosis or dissection