What kind of drug do we need to treat BTK arteries in CLI patients?

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What kind of drug for BTK?

What we know for sure now…….

Followed by
- Fanelli F et al; DEBELLIUM Trial (J Endovasc Ther. 2012 Oct;19(5):571-80)
  - Multilevel treatment (SFA/BTK: 24.8% BTK lesions)
  - Late lumen loss was lower in the DEB group (0.55±1.4 vs. 1.6±1.7 mm, p=0.05)
  - TLR was necessary in 6.1% of the DEB group vs. 23.6% of the POBA group (p=0.02)
- Listro F et al; DEBATE-BTK Trial; (Circulation. 2013 Aug 6;128(6):615-21)
  - 100% Diabetics, 100% CLI and BTK only
  - TLR Rate; 12 (18%) DCB versus 29 (43%; p=0.002) POBA

With great enthusiasm we jumped into the first RCT!
IN.PACT DEEP trial

Great enthusiasm with FIH!

First Experience With Drug-Eluting Balloons in Infrapopliteal Arteries
A Schmidt et al; JACC 2011
- 109 limbs (lesion length 177 mm)
- 17.45% patients with RF category 3
- 3 m angiography at showed a restenosis in 27.4% (19.1% had restenosis of more than 50%, and 8.3% were totally occluded)
- Only in 9.5% of all angiographically followed up arteries was the entire treated segment re-stenosed or re-occluded.
- At 1 year (91 limbs)
  - Complete wound healing occurred in 74.2%,
  - Limb salvage of 95.6%

M Jaff JACC September 2011, 1110-1111:
The Breakthrough Balloon for Critical Limb Ischemia?

Disclosures
Consulting/Honoraria
- Medtronic
- BARD
- Spectranetics
- Intact Vascular
- Soundbite Medical
- Biotronik
- Bayer
- Daiichi
- Böhringer Ingelheim
- Astra Zeneca
What kind of drug for BTK?
What we know for sure now......
Inconsistent data so far from trials comparing DCB/POBA in BTK
RCTs changed the landscape
Equivalent or inferior/harmful results

Biolux II

What are the differences between DCB and PTA in any lesion-specific angioplasty? a year

Impact Deep

Drug-Coated Balloons for Revascularization of Infrapopliteal Arteries: A Meta-Analysis of Randomized Trials
S. Cassese, et al JACC 2016
• A total of 641 patients in 5 trials received DCBs (or control therapy)
• Median follow-up: 12 months.
• Patients treated with DCBs had:
  – Similar risk for target lesion revascularization
  – Similar risk for amputation
  – Similar risk for death
  – Similar risk for major adverse events
• Lesions treated with DCBs showed lower late lumen loss (weighted mean difference 0.41; 95% CI: 0.79 to 0.03; p = 0.04) compared with those treated with control therapy.

Drug for BTK: ATK is not for BTK

Favorable Angiographic Outcome After Treatment of Infrapopliteal Lesions With Drug-Coated Balloons Without Clinical Benefit: What We Learn From a Meta-Analysis*
Thomas Zeller, MD, Michael R. Jaff, JACC 2016
• Only the 3 uncontrolled studies using the IN.PACT Amphirion DCB resulted in superior LLL outcomes
• Both independently core laboratory adjudicated and fully industry funded studies found identical LLL outcomes for the DCB and PTA cohorts
• In summary, despite the superior angiographic outcome defined as LLL in this meta-analysis the performance of DCB in infra-popliteal lesions remains controversial.
• In particular the independently controlled studies did not result in any proof of efficacy of short-term balloon-based paclitaxel release to the wall of infrapopliteal arteries

Drug for BTK: ATK is not for BTK

DCB are still a controversy at this level!
Did we screw up this technology by not performing a correct procedure?

Early Recoil After Balloon Angioplasty of Tibial Artery Obstructions in Patients With Critical Limb Ischemia
Baumann et al. J Endovasc Ther February 2014 vol. 21 no. 1 44-51
Results:
• Elastic recoil: 29/30 patients (97%)
• Mean luminal compromise: 29%
• Acute lumen gain: 1.77 mm (2.00 mm - 0.23 mm)
• Subacute lumen loss (15 min.): 0.53 mm (2.00 mm - 1.47 mm)
Author’s Conclusions:
 Early recoil is frequently observed in CLI patients undergoing tibial angioplasty and may significantly contribute to restenosis.
 These findings support the role of dedicated mechanical scaffolding approaches for the prevention of restenosis in tibial arteries.

Drug for BTK

Possible explanations for failure/PAST
In.Pact DEEP findings
• Some important differences at baseline:
  – Pre-treatment lumen area (DCB vs. PTA): 12.2 vs 21.8 mm² (p<0.001)
  – In-stent lumen area (DCB vs. PTA): 12.76 vs 20.87 mm² (p<0.001)
  – In-stent procedural complications (DCB vs. PTA): 3.7% vs 0.9% (p<0.05)
• Why low angiographic follow-up compliance (~10%?)
• Paclitaxel Patients in In.Pact DEEP did better than expected

Past generation DCB Technologies?
• DCB technology: procedural strategy (Transfer phase)
• Paclitaxel reservoir: anti-proliferative

Drug for BTK

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Drug for BTK/2018

**What attempts have been made to solve controversies?**

**Different drugs will give better results?**

- **Dexamethasone**
  
  A Phase 1, Multi-Center, Randomized, Double-Bind, Placebo-Controlled, Dose-escalation Study of Vonapanitase Administered Following Angioplasty of a Distal Popliteal, Tibial or Peroneal Artery in Patients With Peripheral Artery Disease

- **Temsirolimus**
  
  A phase 1, multi-center, randomized, double-blind, placebo-controlled, dose-escalation study of vonapanitase administered following angioplasty of a distal popliteal, tibial or peroneal artery in patients with peripheral artery disease.

**Improve Paclitaxel DCBs?**

**Beyond Uptake of Drugs?**

- **Calcium is a barrier**

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**Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs.**

"Well-designed randomized trials with long-term follow-up are needed to compare DEBs with uncoated balloon angioplasties adequately for both anatomic and clinical study endpoints before the widespread use of this expensive technology can be justified."
VESSEL PREPARATION/DCB?

What attempts have been made to solve controversies?
Better Uptake of Drugs? Vessel Prep Arterectomy

OPTIMIZE: Orbital vessel Preparation to Maximize DCB Efficacy in calcified below the knee (BTK) lesions

ADCAT: The ADCAT trial (multicenter, Germany, Austria) is looking at an alternate approach to BTK disease by investigating the impact of upfront directional atherectomy prior to DCB angioplasty compared to DCB alone using the Lutonix 14 DCB.

ENROLLMENT FINISHED

VESSEL PREPARATION/DCB?

Different drugs will give better results? Get rid of calcium

Drug Delivery BTK: AHEAD

Drug for BTK/2018......

New drugs (Sirolimus/everolimus instead of paclitaxel)
Additional treatment technologies
Debulking
Trying to get rid of calcium as a barrier
New ways of applying the drug (Limbo)

First Patient enrolled on November 10th 2016 by Dr. Jhaid Mustapha