Biology of in-stent restenosis and rational for debulking

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ISR-complexity
• The local arterial response to stenting as demonstrated by experimental animal and human autopsy studies follows a response-to-injury sequence of events, similar to wound healing.

Inoue S, et al JVS 2002;35:672-678
ISR

- First 3 days:
  - Platelet and fibrin deposition around struts
  - Initial acute inflammatory cell response
- Acute inflammation subsides followed by a granulation tissue response with neovascularization, smooth muscle cell migration and proliferation, and replacement of acute inflammatory cells by chronic inflammatory cells by 2 to 4 weeks: proliferating smooth muscle cells are seen in the early neointima and are associated with organizing thrombus and a thin extracellular matrix.

Inoue S, et al  JVS 2002;35:672-678
After 30 days the presence of fibrin and chronic inflammation may persist, and the neointima is enriched further by smooth muscle cells and extracellular matrix.

The formation of intimal hyperplasia (restenosis) consists of three different processes: cell replication, cell migration, and accumulation of extracellular matrix in the arterial wall.
The extracellular matrix molecules are synthesized by neointimal smooth muscle cells

Extracellular matrix is composed of a variety of molecules, including collagen (type I and III), elastin, glycoproteins, and proteoglycans (versican, biglycan and decorin)

ECM accumulates mainly around stent struts and in the outer intima

Inoue S, et al  JVS 2002;35:672-678
ISR

- Major histological findings
  - In-stent restenotic lesions are complex and differ significantly from de-novo atherosclerotic lesions
  - In-stent restenotic lesions are heterogeneous and consist primarily of collagen and smooth muscle cells
  - Innermost intimal layer of dense smooth muscle cell tissue and an outermost intimal layer that can be described as a cell-poor scaffold or “sponge” comprised of collagen

Inoue S, et al JVS 2002;35:672-678
• Major histological findings
  – Outermost intimal layer is the largest volume constituent of an in-stent restenotic lesion
  – Calcium is rare in in-stent restenotic lesions
  – Thrombus can be present, but typically constitutes a small part of the total volume (exception: acute occlusions that occur within a short time frame after stent placement)
The problem of ISR

Cellular reaction
Extra-cellular matrix (ECM) > 50% of total volume
(Thrombus)

Inoue S et al, JVS 2002;35:672-678
ISR

• ISR lesions are heterogeneous nature
  – Cell-dense intimal layer
  – Cell-poor hydrated matrix in the outer intima to the stent struts
  – “rubbery” in consistency
  – The extracellular matrix accounts for 50% of the total volume of neointimal restenotic lesions

Inoue S, et al  JVS 2002;35:672-678
The problem of ISR

Fully expanded stent
ISR and DEB

- Multiple studies showed benefit of DCB vs. PTA

**DCB in SFA-ISR**
- N = 39
- ISR length = 8.3 cm

**DEBATE ISR**
- N = 44
- 100% DM, 75% CLI
- ISR length = 13.2 cm

**FAIR**
- RCT DCB vs. PTA
- N = 119
- ISR length = 8.2 cm

**IN.PACT vs. PTA historical cohort**
- Primary patency at 2y (0.046)
- TLR: 13.6%, Restenosis: 19.5%

Virga V et al. JACC Cardiovasc Int 2014
Liistro F et al. JET 2014;21:1-8
Krankenberg H et al, Circulation 2015 Oct Epub
ISR and DEB

Restenosis @ 2 years

Virga V et al. JACC Cardiovasc Int 2014
ISR and laser ELA (PATENT)

Schmidt A et al, JET 2014;21:52-60

Cumulative Survival, %

<table>
<thead>
<tr>
<th>Tosaka Class</th>
<th>1 Month</th>
<th>6 Months</th>
<th>12 Months</th>
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<tr>
<td>At risk</td>
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<tr>
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<tr>
<td>Class III</td>
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<td>19</td>
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</tbody>
</table>

Freedom from TLR
Randomized Controlled Study of Excimer Laser Atherectomy for Treatment of Femoropopliteal In-Stent Restenosis

Initial Results From the EXCITE ISR Trial (EXClmer Laser Randomized Controlled Study for Treatment of FemoropopliTEal In-Stent Restenosis)

Eric J. Dippel, MD,* Prakash Makam, MD,† Richard Kovach, MD,‡ Jon C. George, MD,§ Raghotham Patlola, MD,∥ D. Christopher Metzger, MD,¶ Carlos Mena-Hurtado, MD,¶ Robert Beasley, MD,# Peter Soukas, MD,** Pedro J. Colon-Hernandez, MD,†† Matthew A. Stark, PhD,‡‡ Craig Walker, MD,§§ on behalf of the EXCITE ISR Investigators
ISR and ELA

ELA+PTA: less complications, lower TLR rates, higher Primary Patency rates vs. PTA

- 250 Patients (169 ELA+PTA vs. 81 PTA)
- Mean ISR length: 19.6±12.0 vs. 19.3±11.9 cm
- Occlusive ISR: 30.5% vs. 36.8%

Dippel E et al JACC Cardiovasc Int 2015;8:92-101
ISR and ELA/DEB

- 14 patients; mean age 78 ± 6.5 years
- Mean lesion length treated 133.2 mm ± 107.2 mm (range 10 mm – 380 mm)
- Tosaka class I n=2, Tosaka class III n=12 (85.7%)
- Mean time to occurrence of restenosis after initial treatment 8.6 months ± 4.7 months (range 2 – 18 months)
- Distal embolization n=2
- Mean clinical follow-up (n=14) 19.1 months ± 8.7 months (range 9 months – 38 months)
- TLR n=1 (at 3 years after the ISR treatment)

van den Berg JC et al, JIC 2014;26:333-337
ISR and ELA/DEB

• Duplex follow-up (n=12) 19.4 months ± 9.4 months (range 9 months to 38 months)
  – Binary restenosis (>50%) n=1 (@36 months; same patient as TLR)
  – 25-50% stenosis n=4 (mean FU 25 months; range 19-38)
  – No signs of neo-intimal hyperplasia n=7 (mean FU 14.3 months; range 9-19).

• In the patients with critical limb ischemia (n=7) no major amputations were needed

van den Berg JC et al, JIC 2014;26:333-337
ISR and ELA/DEB

100% Occlusive (Tosaka III) ISR with mean ISR treated length: 22.4±9.4 cm vs. 25.9±8.7 cm

12-month Primary Patency: 66.7% vs. 37.5% (p=0.01)

Gandini R et al, JET 2013;20:805-813
ISR and ELA/DEB

Patency translated into significant TLR reduction, lower overall MAE and higher 12-month healing rates

Gandini R et al, JET 2013;20:805-813
Conclusions

• ISR lesions have a unique morphology (the majority of the volume being extra-cellular matrix)

• ISR lesions tend to feel “spongy” and recoil quickly

• PTA/DEB alone will not address the ECM

• Debulking is essential, with use of DEB to prevent mid-to-long term recurrence
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