Novel Therapies for Vascular Access Dysfunction: Optiflow Device, Gene Therapy, and Sirolimus Wrap

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Objectives

- Pathology and Pathophysiology of AVF and AVG Dysfunction
- Novels Therapies
  - Endothelial Cell Implants
  - Elastase
  - Local Gene Delivery Therapy
  - Sirolimus Wrap

Neointimal Hyperplasia Characteristic Lesion of Dialysis Access Dysfunction

Roy-Chaudhury, et al. JASN, 2006 and Lee et al. ACKD, 2009

Hemodynamic and Vascular Biology Interactions:
A Challenge and an Opportunity

Optimize Upstream Hemodynamics

Optimize Downstream Biology

Goals of Therapies to Target Downstream Biology

- Promote Vasodilatation
- Inhibit Neointimal Hyperplasia
Types of Drug Delivery Systems to Treat Vascular Access Stenosis

- Systemic
- Local Drug Delivery
  - Perivascular ("outside to inside")
  - Endovascular ("inside to outside")

Adventitial Cells Migrate to the Intima

After vascular injury adventitial fibroblasts migrate into intima where they become myofibroblasts or contractile smooth muscle cells

Roy-Chaudhury P. et al, JASN, 2006

Principles of Novel Perivascular Local Delivery Therapies

- Drug targets downstream biology
- Drug applied directly to adventitia to block adventitial activation of fibroblasts
- Drug applied locally near or at site of vein-artery (AVF) or vein-graft (AVG) anastomosis
  - Directed at the site of vascular injury with minimal systemic toxicity
- Gradient of drug concentration (highest at adventitia and lowest at endothelium)

Endothelial Cell Implants

Optimizing Downstream Biology: Perivascular Endothelial Cell Implants

- Rationale behind this approach is that the endothelial cell is not just a lining cell but also a cell that produces a slew of beneficial mediators (NO and prostacyclin)
- Just need to deliver ECs to a site near the region of stenosis and the beneficial mediators will do the rest!

Edelman and Negretti J Vasc Res 2003

Optimizing Downstream Biology: Perivascular Endothelial Cell Implants (Vascugel) in Diabetic Patients

- "V-HEALTH STUDY" (Phase I/II trial)
  - No difference in safety profiles (infection rates)
  - No difference in primary unassisted patency
  - Received FDA approval for Phase III study in 2011

Conte et al, JVS, 2009
Efficacy of Phase II Study of Vascugel

Conte et al, JVS, 2009

Primary Patency

- Vascugel 49%
- Placebo 25%

Assisted Primary Patency

- Vascugel 78%
- Placebo 60%

Safety Data From Phase 2 Study of Vascugel

Conte et al, JVS, 2009

Optimizing Downstream Biology: Perivascular Elastase Administration

- Recombinant elastase
- Applied to the adventitia
- Destroys the elastin in the vessel wall (internal elastic lamina)
- Results in a permanent increase in vessel caliber
- Phase I/II study ongoing in AVF/AVG

Elastase Therapy

Gene Therapy
Optimizing downstream biology: VEGF-D “GENE” therapy (Trinam; Ark Therapeutics)

- VEGF-D adenoviral vectors will deliver VEGF-D to the vessel wall
- Stimulate the production of nitric oxide and prostacyclin
- Inhibit venous stenosis at the GVA with minimal systemic toxicity
- Good safety data from a Phase II study

Biodegradable Collar

Perivascular Delivery of Gene Therapy

Completion of Surgical Placement of Collar

Injection of VEGF-D

Sirolimus Wrap

Efficacy of Sirolimus

- Sirolimus is immunosuppressive with anti-inflammatory and anti-proliferative effects
  - Acts on smooth muscle cells
- Proven utility in suppressing neointimal tissue in stents in coronary artery disease
Coll-R sleeves are wrapped around graft (Coll-R #1) and vein (Coll-R #2) at graft-vein anastomosis.

Kaplan–Meier Analysis of Primary Unassisted Patency and Secondary Assisted Patency

Patient Characteristics and Outcomes

Whole Blood Sirolimus Levels Following Implantation

Individual Outcomes of COLL-Grafts

Future Paradigm for Treatment of Hemodialysis Vascular Access Stenosis
Conclusions

- Adventitial activation may lead to cellular migration from adventitia to media to intima
- Perivascular therapies may target adventitial activation and promote vasodilatation and inhibit neointima development
- Promising perivascular therapies entering phase III trials
- Target therapies to multiple points where vascular injury occurs