Molecular Therapies for Vascular Access

NOTES

Jeffrey H. Lawson, MD, PhD, Durham, NC

Over 300,000 Americans currently require hemodialysis for renal replacement therapy at an estimated annual cost of greater than $1 billion (US). Access graft failure results in significant morbidity and increased hospitalization and mortality for patients requiring renal replacement therapy. Major modes of access failure include thrombosis, infection, graft abuse, and intimal/medial proliferation of the venous outflow tract. To date, only surgical and endovascular interventions have been shown to improve long-term access graft patency. An improved understanding of the biology of outflow vein stenosis has now led to the development of novel molecular therapies that may reduce outflow vein proliferation. These therapies direct specific molecular agents to the outflow vein at the time of surgical anastomosis in hope of altering the proliferative cascade that leads to outflow vein stenosis. Recent data from both animal and phase I human clinical trails have demonstrated that agents that either disrupt molecular proliferative pathways in vascular smooth muscle cells or enhance endothelial cell function have a significant impact on reducing outflow vein stenosis. Agents currently in preclinical and clinical trails include inhibitors of G protein signaling pathways and vascular endothelial growth factor. These agents are currently delivered directly to the outflow vein using strategies that allow for the local delivery of adenoviral vectors at the time of surgery. To date, no systemic side effects of local adenoviral applications have been identified in animals or humans, and a significant reduction in outflow vein proliferation has been observed. These molecular biased strategies may alter the biology of outflow vein stenosis and result in long-term improved graft patency, thus improving the overall care of patients requiring long-term hemodialysis.