

Non-technical Abstract

"Restenosis" is the term which has been used to denote *recurrent* narrowing of a blood vessel after an *isner* successful revascularization procedure, such as percutaneous transluminal angioplasty (PTA). PTA involves the use of a tiny balloon mounted on a catheter that can be advanced under x-ray guidance to the site of a blocked artery. When the balloon is inflated, the blockage - and corresponding obstruction to blood flow - is thereby reduced. Despite the fact that PTA has now been used widely to treat atherosclerotic blockages in the coronary and peripheral blood vessels for nearly three decades, restenosis continues to be a vexing, and consequently expensive, complication of this otherwise effective intervention.

In certain regions of the circulatory system, the incidence of restenosis has been so high that it has seriously limited enthusiasm for the application of PTA. The superficial femoral artery (SFA)/popliteal artery of the leg constitutes one such site. Published reports have established that restenosis may complicate the clinical course of as many as 60% of patients undergoing PTA for obstruction of the SFA.

Because disease of the SFA represents one of the most frequent sites of arterial blockage in the leg, the high incidence of restenosis following PTA of this artery implies that patients in whom blockage of the SFA is causing leg pain upon walking ("claudication") must seek alternative treatment. While bypass surgery may be often used to successfully treat these patients, such surgery is not risk-free, particularly when such patients typically suffer from blockages in the arteries supplying blood flow to the heart (coronary arteries) and/or head (carotid arteries). The cost, recuperation time, and frequent requirement for a patient's native veins (the supply of which is fixed and the need for which may extend to coronary bypass or repeat leg bypass surgery) as bypass conduits constitute additional liabilities of SFA bypass surgery.

The inner lining of the blood vessels is composed of cells called "endothelial" cells. These cells have important protective functions. Specifically, these cells make certain proteins that appear to be important in preventing the formation of blood clots or atherosclerotic plaques that may block blood flow through the arteries. Unfortunately, when a PTA catheter is used to "crush" a blockage in an artery, it also typically destroys the endothelial cell lining at that site. Animal experiments suggest that the relatively long time which may be required for these endothelial cells to grow back over the PTA site may be one of the principal factors responsible for restenosis.

Accordingly, the purpose of this clinical protocol is to document the safety of re-endothelialization, achieved in this case by percutaneous catheter-based delivery of the gene encoding vascular endothelial growth factor (VEGF) in patients with claudication due to SFA obstruction. A secondary objective is to investigate the bioactivity of this strategy for inhibiting restenosis. Patients will be studied pre- and post-PTA by a variety of non-invasive and invasive tests for evidence of safety as well as bioactivity. This preliminary study may yield evidence that gene therapy designed to accelerate re-endothelialization at the site of PTA-induced endothelial disruption may represent a novel strategy for inhibition of restenosis in peripheral as well as coronary artery disease.