

Dilemma of Angiogenesis

An old specter haunted the 72nd annual sessions of the American Heart Association in Atlanta last November—the awful nothingness of the placebo effect. No one could prove whether it was or it was not there, but its presence cast a pall over some sessions that dealt with one of the most promising therapies to date—angiogenesis.

The prospect of growing a new network of blood vessels to feed starving heart muscles energized the American Heart Association meetings 2 years ago. However, there appears to be a dichotomy. Patients report improvement; scientists cannot prove it exists.

“What are we trying to do?” asked Michael Simons, MD, director of the Angiogenesis Research Center at Beth Israel Medical Center in Boston. He identified various types of blood vessel growth as angiogenesis, arteriogenesis, and vasculogenesis. “Which of these processes are we trying to induce? One of them or all of them?”

“How does the process work?” he asked. “What are the appropriate targets for the therapy?”

The discussion at the meeting convened by the Angiogenesis Foundation, a nonprofit organization based in Cambridge, MA, dealt with the following new therapies thought to enhance angiogenesis: gene therapy, application of growth factors to stimulate growth, and transmyocardial or direct myocardial revascularization using lasers to punch holes in the myocardium. Founded in 1994, the Foundation has participated in activities involving the therapeutic potential of antiangiogenesis for the past 5 years.

The Foundation convened the 1999 Consensus Meeting: Clinical Trials in Coronary Angiogenesis to improve understanding of where the field is at the moment and where it is going, according to William Li, MD, the organization’s president and medical director. He said the foundation was set up to be a global information clearinghouse, a specialized research and education institute, and a think-tank for drug development—3 important areas in the consensus meeting.

During the discussion, experts in the field asked as many questions as they answered.

Known factors that make a patient eligible for a trial include the following: the patients who have been entered into clinical trials are not suitable or are not ideal candidates for traditional revascularization, according to Nicolas Chronos, MD, director of the Atlanta Cardiovascular Research Institute, they can have no evidence of malignancy, renal insufficiency, or proliferative retinopathy—all conditions that can in theory be exacerbated by the process of angiogenesis; and they must also have demonstrable ischemia in areas in which revascularization is not possible.

However, Dr Chronos asks, “Should we be putting patients with endogenous collateral circulation in these groups? Should we measure endogenous angiogenesis proteins?” Should doctors evaluate patients in an attempt to exclude those at risk of sudden death? These are difficult criteria. And then, there is the influence of the placebo effect.

As Richard Kuntz, MD, an associate professor at Harvard Medical School and chief of the division of clinical biometrics at Brigham and Women’s Hospital in Boston, said, patients who enter the trials have no revascularization option and are maximally treated with medication. “They are desperate. They are interested in alternate approaches to their disease and vulnerable to placebo effects. Chronic angina patients don’t die. They just suffer.”

According to Dr Kuntz, outcomes are difficult to define. “We struggle with endpoints.” Measurements can include treadmill tests, tests of myocardial function, thallium perfusion scans, and quality of life issues. Randomized clinical trials are critical to the future of angiogenesis treatment. “We can’t expose patients to the invasive procedures of this therapy if we don’t know how it works.”

The uncertainty of the researchers was not apparent a day later when several researchers discussed their work with a room full of journalists. Michael J. Mann, MD, of the Brigham and Women’s Hospital in Boston, claimed his study, the Project of Ex-Vivo Vein Graft Engineering Via Transfection or PREVENT, was the first scientifically designed trial of gene therapy with provable benefit.

His study was unusual because the method of introducing the tiny bits of DNA into the tissues of a vein was pressure, which Dr Mann claimed resulted in as much as 89% uptake of the foreign DNA by the vein cells.

In the study, all patients needed a bypass of blocked arteries in the leg. One group received bypass alone. A second group received a vein that had been treated with an EF2 decoy fragment of DNA that was designed to inactivate a growth accelerator in the vein cells, thus repressing the unchecked proliferation that results in blocked and failed grafts. A third group received veins treated with a scrambled DNA sequence that had no effect. The treated veins were in a fluid containing the appropriate pieces of DNA under pressure, a process that took only approximately 10 minutes to complete.

Although the study was designed to test safety, Dr Mann pointed out that the group that received the EF2 decoy-treated graft registered 29% graft failures, whereas the group that received the untreated vein registered 69% graft failures. In the treated group, all failures occurred within 6 months of the surgery.

When Timothy Henry, MD, director of interventional cardiology at Hennepin County Medical Center in Minneapolis, MN, discussed his VEGF in Ischemia for Vascular Angiogenesis (VIVA) trial, he added another layer to the puzzle of that placebo-controlled randomized study.

Last March VIVA seemed to be going nowhere when investigators reported no difference in the exercise performance among patients in the various arms of the study.

One group of 62 patients in the study received placebo infusions that included an initial intracoronary infusion followed by 4-hour intravenous infusions on days 3, 6, and 9. The patients in the low-dose group received $17 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of the vascular endothelial growth factor protein on the same schedule. The high-dose group received $50 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

There were no adverse events in the treated group, according to Dr Henry. However, there were 2 deaths, 3 cancers, and 1 case of retinopathy in the placebo group. Although Dr Henry said he saw a drop-off in the placebo effect, the differences have not yet reached statistical significance. The question is whether the placebo effect would play the same role in a larger trial with less desperate patients. "What are the

best endpoints?" he said. "Two months is too early. I don't think we have hit the peak angiogenic effect at two months."

Valentin Fuster, MD, PhD, immediate past president of the American Heart Association and director of the Cardiovascular Institute at Mount Sinai Medical Center in New York, has chaired the 3 press conferences that have dealt with gene therapy for forms of atherosclerosis since studies began. He said he has seen a steady progression of the science.

The first such session in 1997 demonstrated that "it was possible," according to Dr Fuster. "Last year, it was feasible. Today, it is almost clinically possible."

Elizabeth Nabel, MD, director of the Clinical Research Program of the National Heart, Lung, and Blood Institute in Bethesda, MD, sought to sum up the various kinds of research going into gene therapy of heart disease. In the end, she said translational research such as this frequently makes a circle—going from the laboratory to animal studies to patients trials and then back to the lab where researchers attempt to fine-tune their approach to often difficult issues.

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