Aspirin Resistance Attributed to Noncompliance

BY JANE SALODOF MACNEIL
Senior Editor

ATLANTA — Noncompliance is the main cause of aspirin resistance, according to investigators who studied aspirin response in 230 people, most of whom had a history of myocardial infarction.

The study initially classified up to 30% of the participants as aspirin resistant, but in the end, only 4% of 185 people in whom aspirin response was measured met a conservative definition of aspirin resistance. These seven patients were determined to have a low response to aspirin. One person violated the study's protocols by taking a nonaspirin nonsteroidal anti-inflammatory drug (NANSAID) that would have interfered with aspirin's effects.

Among participants who complied with the protocol, aspirin responses were normally distributed, Dr. Kenneth A. Schwartz reported at the annual meeting of the American Society of Hematology. No difference was seen between those with a history of MI and those in a control group.

"In my way of thinking, there are no people other than NANSAID people that you can label as truly aspirin resistant based on genetics or some other prior inability to respond to aspirin," Dr. Schwartz, professor of medicine, Michigan State University, East Lansing, said in an interview alongside his poster.

Physicians should focus on compliance rather than resistance, he said, recommending that they test patients for aspirin use when they appear to be resistant. "In our studies, we found about 30% of patients could be labeled as aspirin resistant, and 90% of them [62 of 69 patients] were noncompliant," he said.

Dr. Schwartz and his colleagues started with 230 evaluable individuals, all of whom were told not to take aspirin for 7 days. After the 7 days, they removed 45 from the study because they were not compliant with the protocol during the withdrawal period.

This left 185 participants—146 with a history of MI and 39 normal controls—in whom aspirin response was measured with platelet prostaglandin agonist (PPA) stimulated light aggregometry. The participants' average age was 61 years, and 63% were men. Blood was drawn twice: immediately after the 7-day washout period, and then 2 hours after a nurse observed each participant ingesting 365 mg of aspirin.

"These patients were very special because we were sure they were off aspirin because we checked with arachidonic acid," Dr. Schwartz said. "And we were sure that they were on aspirin … because we watched them take the aspirin. And that's why we got a nice normal curve."

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DR. SCHWARTZ

Arachidonic acid testing can reveal whether a patient is taking aspirin, which inhibits cyclo-oxygenase-1–mediated events leading to platelet aggregation. A relatively new test, PPA-stimulated light aggregometry allowed the investigators to measure the extent of aspirin-induced platelet inhibition. To define net aspirin response, they subtracted the slope of each patient's post-aspirin PPA light aggregation curve from the curve recorded when the patient was aspirin free.

While the seven low responders had a decrease that was less than one standard deviation, the investigators suggested they might not be a distinct population but the bottom of a normal bell-shape distribution curve. "If there was a separate group of patients that were aspirin resistant, this would show a subgroup in which there was a poor response, and we don't see that," he said.

In an earlier phase of the study, he said, arachidonic acid failed to show the expected aspirin inhibition in 17 of 192 heart attack patients who had been prescribed aspirin. All but one showed aspirin inhibition when they were retested 2 hours after being observed taking aspirin, however.

The 1 patient admitted to taking a NANSAID in violation of the protocol, leaving the investigators to conclude that the other 16 were not aspirin resistant but rather were noncompliant with their prescribed aspirin use.

Dr. Schwartz said he did not know why patients were not compliant but that they should be counseled about the importance of aspirin to their survival. "If you don't get your aspirin, you don't get your benefit," he said. "Aspirin is one of the most effective drugs we have in terms of platelet inhibition." ■

CD34+ Stem Cell Transplant Helps in Refractory Angina

BY NANCY WALSH
New York Bureau

NEW YORK — Therapeutic neovascularization through the intramyocardial administration of autologous CD34+ stem cells is a promising approach in patients with refractory ischemia, Dr. Timothy D. Henry said at a conference on cell therapy and cardiovascular diseases.

Many patients with severe coronary artery disease experience persistent, disabling angina despite the use of antianginal drugs and mechanical revascularization, and few good options exist for these patients at present, according to Dr. Henry, who is chief of research, Minneapolis Heart Research Foundation, Minneapolis.

Preclinical studies suggested that neovascularization is possible in chronic ischemia following the administration of autologous endothelial progenitor cells, and particularly when cells expressing the CD34+ marker were used. A pilot study has now provided evidence that such an approach is safe and may result in symptomatic improvements in angina symptoms, Dr. Henry said.

The double-blind, placebo-controlled study included 24 patients comprising 5 women and 19 men, whose mean age was 62 years. All had Canadian Cardiovascular Society (CCS) class III or IV angina, were not candidates for conventional revascularization, had failed on optimal medical therapy, and were on at least two antianginal medications.

Initially all patients underwent stem cell mobilization with the administration of granulocyte colony-stimulating factor for 5 days, at which time leukapheresis was performed and the CD34+ fraction of mononuclear cells were isolated.

At 3 months after injection, the number of episodes of angina per week fell from 21 to 10 in the treated group, and rose from 21 to 27 in the placebo group.

They then underwent cardiac navigation using NOGA electromechanical mapping and intramyocardial injection of the CD34+ cells or placebo into the ischemic zone, and were followed for 12 months.

The treatment was well tolerated, with no serious adverse events being attributed to the cell therapy, Dr. Henry said. One patient in the placebo group developed ventricular tachycardia during the mapping procedure, but was cardioverted successfully.

At 3 months, the number of episodes of angina per week fell from 21 to 10 in the treated group, and rose from 21 to 27 in the placebo group. By 6 months, the number of episodes per week had fallen to 9 and 16 in the treated and placebo groups, respectively (Circulation 2007;115:3165-72).

By 6 months, 50% of patients in the treated group had experienced an improvement by at least two CCS classes, as had 33% of placebo patients.

Results on single-photon emission computed tomography (SPECT) were mixed, showing some improvement at 3 months but none at 6 months, Dr. Henry said. "One of the things holding us back in treating patients with chronic refractory ischemia is the lack of a gold standard to measure myocardial blood flow," he said.

Moreover, improvements in exercise tolerance were modest at best, increasing 0.3 minutes and 0.5 minutes in the placebo and active treatment groups at 3 months, respectively.

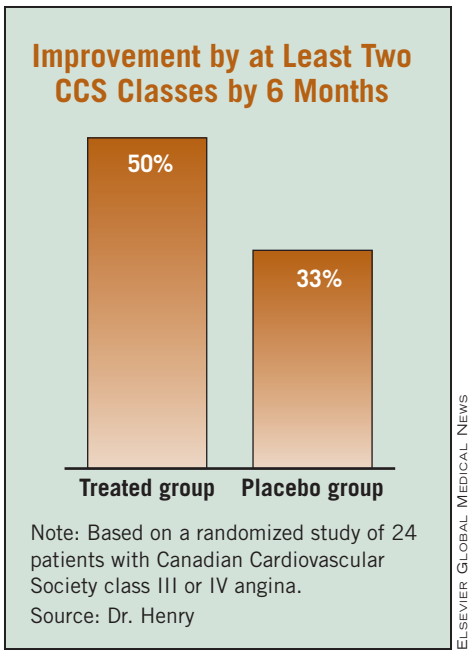
Previous trials of various therapies for refractory angina also have failed to demonstrate improvements in exercise tolerance. For example, in an analysis of pooled data from the Angiogenic gene therapy (AGENT) 3 and 4 studies, which evaluated the intracoronary administration of Ad5FGF-4 in patients with chronic angina, there was no significant difference between the active treatment and placebo on the primary end point of change from baseline exercise time at 12 weeks. However, the incidence of angina and worsening angina was significantly less in patients receiving the gene therapy, at 18%, compared with those receiving placebo, at 25% (J. Am. Coll. Cardiol. 2007;50:1038-46).

"As far as placebo-controlled trials that show improvement in exercise time in patients with refractory angina, for angiogenesis there are none, for enhanced external counterpulsation there have been none, for percutaneous transmyocardial laser revascularization there have been none, and for novel drug therapy, there have been none," Dr. Henry said. "If you ask the patients what the problem is, they say it's chest pain."

Therefore, a larger randomized trial of CD34+ stem cells that has recently completed enrollment has, as its primary efficacy end point, frequency of angina episodes.

The study protocol calls for 150 patients aged 21-80 years who have CCS functional class III or IV refractory angina. Following the intramyocardial injection of autologous stem cells or placebo, patients will be followed up with MRI and SPECT at 6 and 12 months.

"It's important to remember that this is a very challenging patient population, where bypass didn't work, PCI didn't work, and medical therapy didn't work, and for whom we don't have great options now. Will CD34+ therapy be a better option? Certainly the phase I trial was suggestive, and we're excited about seeing the results of the phase II trial," said Dr. Henry, who is a consultant to Baxter Healthcare, the study sponsor. ■



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