Genetic Test Cuts Need for Posttransplant Biopsy

The patients with lower scores on the test showed no signs of rejection; those with higher scores did.

BY MITCHEL L. ZOLER
Philadelphia Bureau

MADRID — A blood test that measures the activity of genes that help control immune response to a transplanted heart was able to reliably rule out future organ rejection in a study with 192 patients.

"We believe that these findings may pave the way to a reduced need for protocol-mandated cardiac biopsies" in patients who have received a heart transplant, Dr. Mandeep R. Mehra said at the annual meeting of the International Society for Heart and Lung Transplantation. The results also may point to a new approach for assessing the adequacy of steroid treatment for a variety of diseases and conditions.

A new analysis of data collected in a previously reported study showed that about one-third of the heart-transplant patients involved had low scores on a specially designed gene expression test performed 30 or more days following transplantation. These low-score patients showed no sign of rejection in biopsies taken during the next 3 months, whereas patients with higher scores had an incidence of biopsy-proven rejections of about 60% over the subsequent 3 months.

On the basis of these results, Dr. Mehra said that he would be comfortable skipping cardiac biopsies in patients with low gene expression scores in tests run 30-180 days after transplantation. A low score was defined as 20 or less on a scale of 0-40 in the AlloMap test, which is marketed by XDx Inc.

XDx sponsored the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study, which was designed to assess the ability of the gene expression test to diagnose rejection of a transplanted heart as it was occurring. The efficacy of the test for this purpose was first reported in 2005 at the annual meeting of the International Society for Heart and Lung Transplantation, and was published last January (Am. J. Transplant. 2006;6:150-60). Dr. Mehra and his associates reanalyzed the data from this study to see if the gene expression test could also predict future rejection episodes. Dr. Mehra received research support from and is a consultant to XDx.

The new findings are "very exciting and show a lot of promise," commented Dr. A.G. Kfoury, medical director of the UTAH Cardiac Transplant Program at LDS Hospital in Salt Lake City.

"If we can avoid cardiac biopsies it would be a big help. Biopsies are very hard on patients," commented Dr. Elizabeth H. Hammond, professor of pathology and an expert on rejections following heart transplants at Intermountain Healthcare in Salt Lake City.

The gene expression test looks at RNA levels in peripheral-blood mononuclear cells to assess the activity of 11 genes involved in five basic activities that affect the immune response to a foreign organ: T-cell priming, platelet activation, steroid responsiveness, stem cell activity, and cell migration. The panel was designed to flag active rejection, and not to predict rejection before it actually appeared, said Dr. Mehra, chief of the division of cardiology at the University of Maryland in Baltimore.

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DR. MEHRA

The reanalysis of CARGO data involved two separate assessments. First was a case-control analysis that included 39 of the patients in CARGO who eventually had heart rejection, and 65 who did not. The overall profile of both groups did not differ by age, gender, or race, and the steroid doses administered prior to any diagnosed rejections were similar. Dr. Mehra and his associates reviewed the results of gene expression profiles that were tested starting 1 month after transplant and retested periodically out to 1 year after transplant. Each test result was analyzed relative to whether a rejection episode occurred during the 2-12 weeks after the test was made.

Total gene expression scores were significantly lower in the patients who did not have rejections during the several weeks following each test. Test scores were most predictive during the first 6 months after transplantation. In this period, the most informative genes were the three that affect responsiveness to steroid therapy. "This may be a way to assess adequate treatment with steroids," Dr. Mehra said.

The second analysis examined the predictive capacity of 192 consecutive test results that came from all patients in the study during the first 6 months following transplantation. This assessment showed that a gene expression test score of 20 or less predicted the absence of a rejection episode during the subsequent 12 weeks with 99% accuracy, Dr. Mehra reported.

The gene expression test performed consistently well for predicting subsequent rejections during the first 1-6 months after transplantation.

Dr. Mehra noted that the gene-testing panel was developed to measure current rejection. It's reasonable to speculate that efforts to optimize predictive capabilities may identify a different, more effective expression panel.

In addition, the gene expression test may be useful for monitoring the adequacy of treatment with steroids in other types of patients, including recipients of other transplanted organs or those treated with steroids for diseases such as rheumatoid arthritis.

"Until now, we have had no way to measure the adequacy of steroid responsiveness. The gene expression information will allow physicians to tailor the right steroid dose to each patient," Dr. Mehra said. ■

Tacrolimus Gains FDA Approval for Use in Heart Recipients

BY ELIZABETH MECHCATIE
Senior Writer

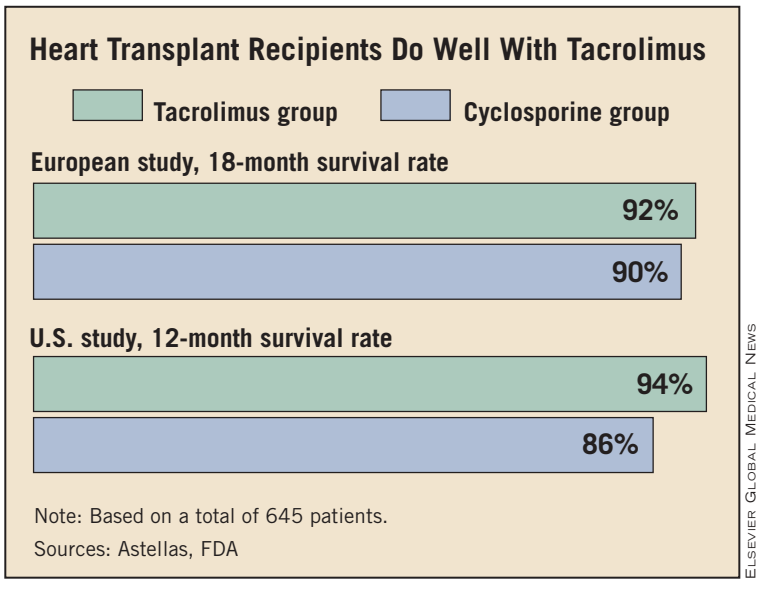
The Food and Drug Administration has approved the immunosuppressant tacrolimus for preventing rejection in heart transplant recipients, on the basis of studies that found similar rates of patient and graft survival in patients on tacrolimus-based regimens and cyclosporine-based regimens.

Tacrolimus, marketed as Prograf by Astellas Pharma US, was previously approved for preventing rejection in kidney and liver transplant recipients and has been increasingly used off label for heart transplant recipients over the past several years.

During this time, "tacrolimus has been gaining favor as the first-line drug of choice," said Dr. Jon Kobashigawa, medical director of the University of California, Los Angeles, heart transplant program, where a switch from a cyclosporine-based regimen to a tacrolimus-based regimen, usually with mycophenolate mofetil (MMF), was made about 5 years ago. After reports found it effective in reversing recurrent or refractory rejection, its use for primary prevention was studied in several trials, which demonstrated that a tacrolimus-based regimen was at least as effective as cyclosporine-based regimens, he said in an interview.

Two studies published in April in the American Journal of Transplantation demonstrated that the tacrolimus-based regimen was more effective in reducing rejection and had fewer side effects than did the cyclosporine-based regimen, said Dr. Kobashigawa, a principal investigator of one of these studies. He has received research grants and speaker honoraria from Astellas, and is on the company's scientific advisory board.

The incidence of rejection has decreased significantly at the UCLA program since the switch to tacrolimus and MMF, which "seems to have the best profile in terms of efficacy and lowest side effects," he said. The major side effect differences with a tacrolimus-based regimen compared with cyclosporine are decreases in renal dysfunction, hyperlipidemia, and hypertension, which "all play a role in long-term outcome."



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Centers in the United States that still use cyclosporine-based regimens for heart transplant recipients will find it easier to switch now that heart transplantation is a primary indication, which will help insurance coverage, he said.

Prograf is marketed in Europe and Japan and is commercially available in about 70 countries, according to Astellas, the company that was created from the merger of Fujisawa Pharmaceutical Co. and Yamanouchi Pharmaceutical Co. last year. The U.S. approval pertains to both the capsule and intravenous formulations.

According to information provided by Astellas and the FDA, the March approval was based on two open-label, randomized studies comparing tacrolimus-based and cyclosporine-based immunosuppression in 645 primary orthotopic heart transplant recipients. In the European study, nearly 92% of patients and grafts had survived 18 months after transplantation, compared with nearly 90% of those who received cyclosporine-based regimens. In the U.S. study, 94% of patients and grafts survived at 12 months after transplantation, compared with 86% among those on the cyclosporine-based regimen.

Tacrolimus is associated with an increased risk of neurotoxicity, renal function impairment, infection, and posttransplant diabetes, and is associated with an increased risk of malignancies, "notably of nonmelanoma skin cancers," the FDA statement said.

Another regimen for preventing heart transplant rejection—a combination of everolimus (a proliferation signal inhibitor) and cyclosporine—is under review at the FDA, but uncertainty over its adverse renal effects has held up approval in the United States. Data on the revised regimen from an ongoing European study are expected to be available by the end of this year. ■