



AMERICAN COLLEGE OF SURGEONS

SURGERY NEWS

Trials Compare Efficacy of Lung Transplant Drugs

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON — Two randomized trials shed light on the relative benefits and risks of immunosuppressive drugs in lung transplant patients, until now an understudied group.

In one multicenter study with 172 patients, treatment with sirolimus led to significantly fewer moderate to severe acute rejection episodes than with azathioprine, but was linked to a significantly higher rate of infections, Dr. Sangeeta M. Bhorade reported at the annual meeting of the International Society for Heart and Lung Transplantation.

Results from another study reported at the meeting showed that fewer episodes of bronchiolitis obliterans syndrome (BOS) occurred in lung transplant patients treated with a tacrolimus regimen than in those randomized to a regimen of cyclosporine, said Dr. Hendrik Treede, a thoracic surgeon at the University Heart Center in Hamburg, Germany. BOS is one of the major long-term complications in lung transplant recipients.

"When was the last time we saw this many clinical trials [reported at one meeting] in lung transplant patients? Never," commented Dr. Jason D. Christie, a pulmonologist and lung trans-

plant specialist at the University of Pennsylvania in Philadelphia.

The typical immunosuppression regimen for lung transplant recipients includes a calcineurin inhibitor, either tacrolimus or cyclosporine, an antiproliferative drug, such as azathioprine or mycophenolate mofetil (MMF), and a corticosteroid. "But there is no established standard of care, and none of these drugs have [Food and Drug Administration] approval for use in lung transplant patients," Dr. Christie said in an interview.

Dr. Bhorade's study was conducted at eight U.S. centers that used a background regimen of tacrolimus and prednisone, and then randomized patients to additional treatment with sirolimus or azathioprine. Astellas, which markets tacrolimus (Prograf), sponsored the study. Dr. Bhorade, medical director of the lung transplant program at the University of Chicago, has received research support from Astellas.

The study's primary end point was freedom from acute rejection episodes after 1 year of treatment. Rejection episodes of all severity levels occurred in about 50% of the 92 patients treated with azathioprine and in about 40% of the 80 patients treated with sirolimus, a difference that was not statistically significant. But moderate to severe acute re-

jection episodes occurred in 20% of the sirolimus-treated patients and in 28% of the azathioprine patients, a significant difference. A total of 21 moderate to severe episodes occurred in the sirolimus patients versus 39 in the azathioprine group, Dr. Bhorade reported.

Sirolimus treatment was linked to more bacterial and fungal infections but fewer viral infections, particularly by cytomegalovirus.

The rate of BOS was similar in the two treatment groups after 1 year, but the BOS incidence after 3 years of treatment is a more standard measure of graft durability. Sirolimus treatment was also linked with higher serum levels of cholesterol and triglycerides, a slightly higher rate of serious adverse effects, and a higher rate of early discontinuation of therapy.

Better results with sirolimus treatment will depend on finding ways to identify the patients who will best tolerate the drug. Longer-term follow-up of these patients, out to 3 years, is also needed, Dr. Bhorade said.

In Dr. Treede's study, which was done at 14 centers in Europe and Australia, all patients were treated with MMF and a steroid and were randomized to treatment with either tacrolimus or cyclosporine. This study was also funded by Astellas, but was re-

searcher initiated.

After 3 years, the rate of freedom from an acute rejection episode was 33% among 120 patients treated with tacrolimus and 27% among 120 patients treated with cyclosporine, a difference that was not statistically significant, said Dr. Treede. The incidence of BOS was 20% in the cyclosporine-treated patients and 11% in the tacrolimus group, a difference that just missed statistical significance ($P = .058$). The rate of overall survival was also similar in the two groups, and there was also no difference in the incidence of adverse events,

such as infections or renal impairment, he added.

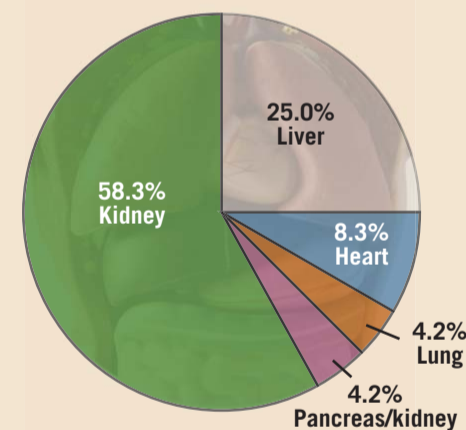
No drug in these trials was significantly superior to its comparator for the primary end point. But the findings supported the concept that immunosuppressive regimens should be tailored to each patient's specific needs, such as the susceptibility to infection, Dr. Bhorade said in an interview.

For example, if a lung transplant patient has had several infectious complications, "you may want to hold off on drugs that can predispose to infections, like sirolimus," she said. ■

DATA WATCH

2006 Organ Transplant Immunosuppressant Market

Total market = \$4.8 million



Source: Kalorama Information

ELSEVIER GLOBAL MEDICAL NEWS

High Cholesterol Ups Vasculopathy Risk After Heart Transplant

BY MITCHEL L. ZOLER
Elsevier Global Medical News

BOSTON — Higher levels of hypercholesterolemia despite statin therapy were linked with an increased risk for vasculopathy in a series of 301 heart transplant patients treated at one center.

The findings suggest that heart transplant patients who maintain elevated levels of serum cholesterol despite standard statin treatment need a more aggressive regimen, Dr. Jignesh K. Patel said at the annual meeting of the International Society for Heart and Lung Transplantation.

The safety and efficacy of a 40-mg/day dosage of pravastatin for reducing the risk of cardiac allograft vasculopathy (the equivalent of coronary artery stenosis in heart transplant patients) was first established in a landmark 1995 study done at

the University of California, Los Angeles (N. Engl. J. Med. 1995;333:621-7). But until now there was no evidence that heart transplant patients who maintain an elevated level of serum cholesterol despite statin treatment continue to face an increased risk of vasculopathy.

This possibility was examined in 301 heart transplant patients treated at UCLA during 1994-2000 who survived more than 1 year posttransplant. Serum cholesterol levels in these patients were measured at 3, 6, and 12 months after transplantation, and the mean serum level of total cholesterol in these three measurements during this first year was correlated with outcomes during the subsequent 4 years.

Immunosuppressive and statin regimens among all patients were similar, but total cholesterol levels varied widely. A level of less than 150 mg/dL occurred in 20%, a

level of 151-200 mg/dL was seen in 27%; a level of 201-250 mg/dL in 30%; and a level greater than 250 mg/dL in 23%.

The analysis showed no differences in the 5-year rate of survival, or in total major adverse coronary events, including nonfatal myocardial infarction and heart failure. The survival rates ranged from about 83% to 92% across the four subgroups, and the rates of freedom from major nonfatal coronary events ranged from 79% to 89%.

But the 5-year incidence of vasculopathy was 53% in the patients with an average total cholesterol level above 250 mg/dL during the first year, compared with all three of the other subgroups. In the subgroups, the vasculopathy rate ranged from 23% to 31%.

In a multivariate analysis that controlled for baseline differences in age, gender,

race, body mass index, and ischemic time during transplantation, a total cholesterol level above 250 mg/dL was a significant predictor of vasculopathy, compared with patients with lower cholesterol levels, said Dr. Patel, associate medical director of the UCLA heart transplantation program.

Pravastatin remains the standard lipid-lowering agent used on all heart transplant patients at UCLA, and is usually titrated up to a maximum daily dose of 40 mg. If a patient's serum cholesterol is above 250 mg/dL despite this dosage, the patient is switched to atorvastatin and again titrated to a maximum dose of 40 mg/day. Based on the new findings, if the total cholesterol level remains above 250 mg/dL despite this treatment, current practice is to add additional lipid-lowering drugs to try to bring the level down to less than 250 mg/dL, Dr. Patel said. ■

'Hospital Compare' Site Adds Patient Satisfaction Data

The CMS database provides the volume of certain elective procedures and the Medicare payment.

BY JOYCE FRIEDEN
Elsevier Global Medical News

ARLINGTON, VA. — Now that the Centers for Medicare and Medicaid has added patient satisfaction data to its Hospital Compare Web site, patients will have more to consider when they are deciding which hospital to use for an elective procedure.

The Web site already included hospital-specific information on clinical measures such as antibiotic prophylaxis before surgery and aspirin upon admission for a heart attack. New patient satisfaction data include items such as nurse communication and hospital room cleanliness.

"This is like Travelocity for health care," said Health and Human Services Secretary

Mike Leavitt. "When people have information and they have choice, they make good choices." Mr. Leavitt spoke at the annual meeting of the Association of Health Care Journalists.

The patient satisfaction data come from the Consumer Assessment of Healthcare Providers and Systems, a survey administered by 2,500 hospitals to patients discharged between October 2006 and June 2007.

The survey included 27 questions about patients' hospital experience, including communication with doctors and nurses, responsiveness of hospital staff, cleanliness and quietness of the hospital environment, and pain management.

The database also will include the volume of certain elective procedures pro-

vided at the hospital as well as what Medicare pays for those procedures (see www.hospitalcompare.hhs.gov). The Centers for Medicare and Medicaid Services (CMS) Deputy Administrator Herb Kuhn said the information will be valuable even if patients already have selected a hospital for an elective procedure.

"There are three reasons people pick a hospital," he said in an interview after Mr. Leavitt spoke. "They heard it was good, it's where their physician spends a lot of his time, or it's convenient to them. We want to add another dimension here for people to understand: Okay, if that's where you're going, what do you know about this place?"

The database also will be a good motivator for hospital improvement, Mr. Leavitt said. "Every health care provider wants to provide high-quality [care]," he said. "Wherever in health care there's robust information about quality and cost, the cost

goes down and the quality goes up."

Mr. Leavitt stressed that CMS was not posting the data in order to punish hospitals that aren't performing as well as others. "This is not about eliminating anyone; it's about improving everyone," he said.

As for whether those hospitals that don't improve might eventually face consequences, "I hope so," Mr. Leavitt said, noting that his tenure as HHS secretary would likely be over by the time that came to pass.

"This is about transparency and accountability. Without consumers and regulators and others having a means of measurement, we continue to reward mediocre—and in some cases, poor—performance. While this is not about eliminating those who are not performing well, we should certainly not assume that those who are poor performers will not be eliminated, either by the marketplace or by those who oversee quality." ■

Agreement Sets Rules For Physician Ratings

BY MARY ELLEN SCHNEIDER
Elsevier Global Medical News

Under an agreement among physicians, consumers, employers, and large insurers, some health plans have agreed to have their physician rating systems audited by independent experts.

The announcement comes after physicians around the country have questioned the methods used by health plans to produce the physician performance ratings for consumers.

Under the voluntary agreement, known as the Patient Charter for Physician Performance Measurement, Reporting, and Tiering Programs, health plans would disclose their rating methods. In addition, physicians would have a chance to review their performance data and challenge it prior to publication.

The project was led by the Consumer-Purchaser Disclosure Project, a coalition of consumer, labor, and employer organizations that support publicly reported health performance information.

Other principles of the Patient Charter state that the measures should aim to assess whether care is safe, timely, effective, equitable, and patient centered. The measures used should also be based on national standards, preferably those endorsed by the National Quality Forum.

The principles of the Patient

Charter do not apply to pure cost-comparison or shopping tools.

Among other health care organizations, the Patient Charter has the support of the American College of Surgeons and the American Medical Association.

Some heavy hitters in the insurance industry have agreed to abide by the principles of the charter, including trade group America's Health Insurance Plans (AHIP), as well as Aetna, Cigna, UnitedHealthcare, and WellPoint.

Other health plans are likely to follow suit, said Susan Pisano, AHIP spokeswoman. Third-party review of rating systems and allowing physicians to review and challenge data before they become public will likely become the industry standard, she said.

"We believe strongly that consumers both want and need good information on health care quality," Ms. Pisano said.

Now that the Patient Charter has laid down the ground rules for how clinical performance measures should be used, the next step is to ensure that physician ratings accurately reflect all the care that is given. This can be challenging, because patients are generally scattered across multiple health plans. Ms. Pisano said the AHIP Foundation is studying how to aggregate data from across different plans to provide a full picture of physician quality. ■

Mafenide Acetate Associated With Fungal Infections in Burn Patients

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — The use of topical mafenide acetate on burn wounds was associated with a higher incidence of fungal infection than was silver sulfadiazine in a retrospective analysis of 111 patients.

The chart review was initiated after physicians at the regional burn center of Miami Valley Hospital, Dayton, Ohio, observed an increase in fungal infections after a protocol change was instituted in which the application of saline soaks for 24 hours followed by silver sulfadiazine 1% cream (Silvadene) was replaced with only the application of mafenide acetate 5% solution (Sulfamylon) as the topical antibiotic of choice for initial antimicrobial therapy.

The change in protocol, which was made in 2002 in an effort to improve patient outcomes, has since been reversed, said research coordinator Ryan Shapiro, on behalf of principal investigator Dr. R. Michael Johnson, at the annual meeting of the American Burn Association.

From 1998 to 2006, 42 patients were treated twice daily with silver sulfadiazine, and 69 with mafenide acetate solution. The silver sulfadiazine group was significantly younger than the mafenide acetate group (mean age, 38 vs. 48 years), less likely to have a central line (16 vs. 43 patients), and more likely to have shorter ICU stays (4 vs. 10 days) and shorter total hospital stays (23.5 vs. 34 days).

Nonsignificant differences be-

tween the silver sulfadiazine and mafenide acetate groups included mean total body surface area burned (27% vs. 29%), inhalation injury (14 vs. 25 patients), and mortality (6 vs. 13 patients).

Univariate analysis showed that patients receiving mafenide acetate solution had twice the rate of burn infection or systemic fungal infection (48%) compared with patients receiving silver sulfadiazine (24%), reported the investigators.

Patients receiving mafenide acetate also had four times the rate of systemic fungal infections (27.5%) compared with patients receiving silver sulfadiazine (7%). Both outcomes were statistically significant.

Significant predictors of fungal infection on univariate analysis included age, length of ICU stay, total length of stay, presence of a central line, and use of mafenide acetate. However, in multivariate logistic regression analysis, only length of ICU stay and total length of stay remained as independent predictors of fungal infection, according to Dr. Johnson, an ACS Fellow who is chief of plastic surgery at Miami Valley Hospital, and his colleagues.

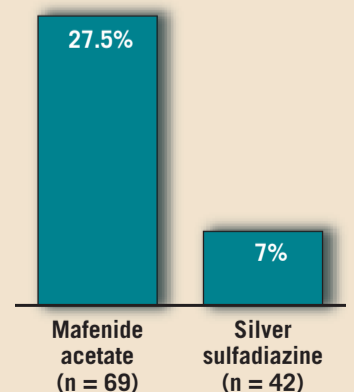
The overall higher fungal infection rate in the series was higher than expected, and could be the result of an increase in the age of patients being treated rather than the choice of topical antibiotic, the investigators

noted. They disclosed no relevant conflicts of interest.

The protocol was changed to using silver sulfadiazine cream in 2006, but mafenide acetate is still used in the burn unit at the physician's discretion, they indicated.

Audience member Dr. Debra A. Reilly, an ACS Fellow who is director of the burn center and a surgeon at the University of Nebraska Medical Center in Omaha, recounted similar problems with mafenide acetate and fungal infections, but cautioned the audience not to discard the drug, calling it a "very useful product" with a long track record. Dr. Reilly suggested adding the antifungal nystatin, with the caveat that it must be combined with mafenide acetate suspension and not mafenide acetate solution. ■

Rate of Systemic Fungal Infection Raised With Mafenide



Note: Based on data for burn patients treated from 1998 to 2006.
Source: Dr. Johnson