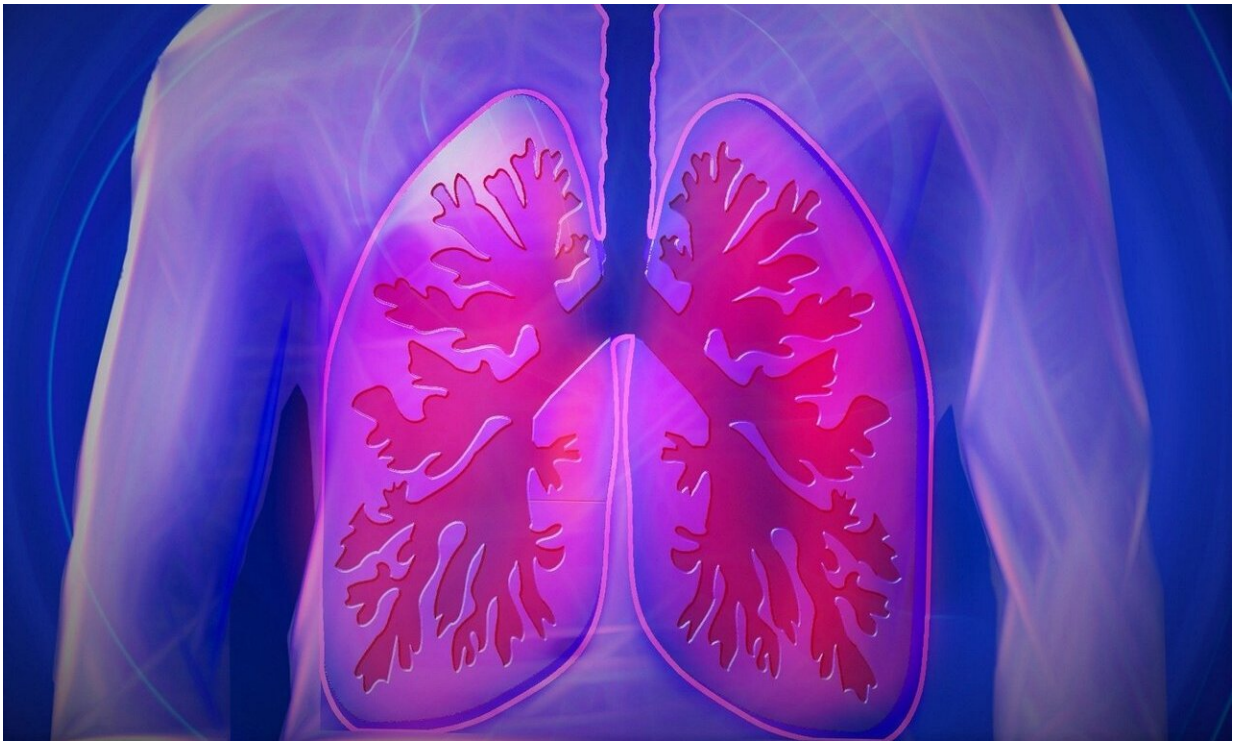
Little-used drug combination may extend the lives of lung transplant patients

August 28 2019



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Lung transplantation can prolong the lives of patients with end-stage lung disease, but the median survival rate after lung transplant is less than six years, which has improved only slightly in recent decades. To see what might help lung transplant recipients live longer, researchers at the University of Maryland School of Medicine (UMSOM) developed a

novel epidemiological analysis of lung transplant data in the United States focused on regimens that prevent the body's immune system from attacking the transplanted lung. The study has identified a drug combination that appears to significantly extend patient survival.

"We postulated that an infrequently used regimen may make a difference in outcome," said Aldo T. Iacono, MD, the Hamish S. and Christine C. Osborne Distinguished Professor in Advanced Pulmonary Care at UMSOM, Medical Director of the Lung Health Program at the University of Maryland Medical Center and senior author of the study, published in *JAMA Network Open*. "What we found could improve survival of lung transplant patients on a larger scale."

To prevent chronic rejection, the most common cause of death after a lung transplant, patients must take immunosuppressive drugs for the rest of their lives. Immunosuppression, in turn, may predispose patients to infections and cancers, the second- and third-leading causes of post-lung transplant death. Few outcome studies have been done in the field of lung transplantation to determine what works best. Further, the U.S. Food and Drug Administration has not approved any immunosuppressive drugs or drug regimens specifically for use in patients with a lung transplant.

Using a database of over 9,000 lung transplant patients maintained by the United Network for Organ Sharing (UNOS), the researchers categorized patients by their immunosuppression regimen and compared survival rates. They singled out an immunosuppressive drug called sirolimus, in a class of drugs called cell cycle inhibitors, based on a few small, long-term studies that found dramatically improved survival, reduced incidence of chronic rejection, and improved lung function in lung transplant patients who took sirolimus.

The database study compared sirolimus outcomes with the most

commonly used cell cycle inhibitor mycophenolate mofetil (MMF). "According to our study, sirolimus appears to offer a survival advantage of almost two years over MMF," said first author Marniker Wijesinha, Ph.D., a UMSOM post-doctoral fellow. "The survival improvement with sirolimus was driven by fewer deaths from the top three causes: chronic rejection, infections, and cancer."

Another immunosuppressive medication, tacrolimus, is currently used in the vast majority of lung transplant recipients and was common to all patients in the study. "The typical regimen consists of three drugs: tacrolimus, a cell cycle inhibitor, and steroids (prednisone)," said Dr. Wijesinha. "The variable in this study was the cell cycle inhibitor."

Sirolimus plus tacrolimus was associated with a better median survival than MMF plus tacrolimus (8.9 years vs 7.1 years).

The majority of patients in the database, nearly 5,800, were given MMF plus tacrolimus, a combination that has become the de facto standard immunosuppression after lung transplant. Sirolimus plus tacrolimus maintenance therapy was provided to slightly more than 200 patients.

One downside for sirolimus, though, is that it interferes with wound healing, a potentially life-threatening complication if the drug is administered in the initial days and weeks following transplant surgery. For this reason, prophylactic sirolimus maintenance therapy is typically not started until three to 12 months after surgery. The researchers accounted for this delayed initiation so sirolimus would not appear to yield a false survival advantage.

"Sirolimus is relatively novel in lung transplantation. Physicians and surgeons in the transplant community have little experience with it," said Dr. Iacono. "Because of that, many physicians may not have confidence in it. However, if we can extend the life of a lung transplant recipient by

two years, you're talking a major accomplishment."

The study also considered induction therapy, an optional addition to maintenance therapy used in over half of transplant centers in the U.S. In induction therapy, patients are given a high dose of immunosuppression at the time of transplantation for a short duration—three to 14 days, with drugs such as basiliximab, daclizumab, alemtuzumab, or antithymocyte globulin.

The group that came out with the highest survival of all combinations was given sirolimus plus tacrolimus for maintenance therapy without induction therapy. These patients lived over three years longer on average than patients receiving MMF maintenance with induction therapy.

"This study illustrates the value of searching through large databases to discern patterns and practices that may not be immediately obvious, but can have a major impact on patient care," said UMSOM Dean E. Albert Reece, MD, Ph.D., MBA, University Executive Vice President for Medical Affairs and the John Z. and Akiko K. Bowers Distinguished Professor. "Further studies of patients undergoing lung transplantation are needed to confirm the findings associated with sirolimus, but this research is a great start."

"A particularly useful direction for a future study would be to investigate the optimal dosages of sirolimus and tacrolimus in lung transplant patients (which may vary according to patient characteristics)," said Dr. Wijesinha. "Our study, unfortunately, could not do this because there were no data on this."

On the clinical front, Dr. Iacono and his UMSOM colleagues have begun applying the findings of the study to their standard treatment regimen for lung transplant recipients, switching to sirolimus in combination with

tacrolimus for long-term prevention of chronic rejection.

More information: Wijesinha M, Hirshon JM, Terrin M, Magder L, Brown C, Stafford K, Iacono A. "Survival Associated with Sirolimus Plus Tacrolimus Maintenance Without Induction Therapy Compared With Standard Immunosuppression After Lung Transplant." *JAMA Network Open*. 2019;2(8):e191027. DOI: 10.1001/jamanetworkopen.2019.10297

Provided by University of Maryland