Inhaled immunosuppressant may increase survival, pulmonary function after lung transplant

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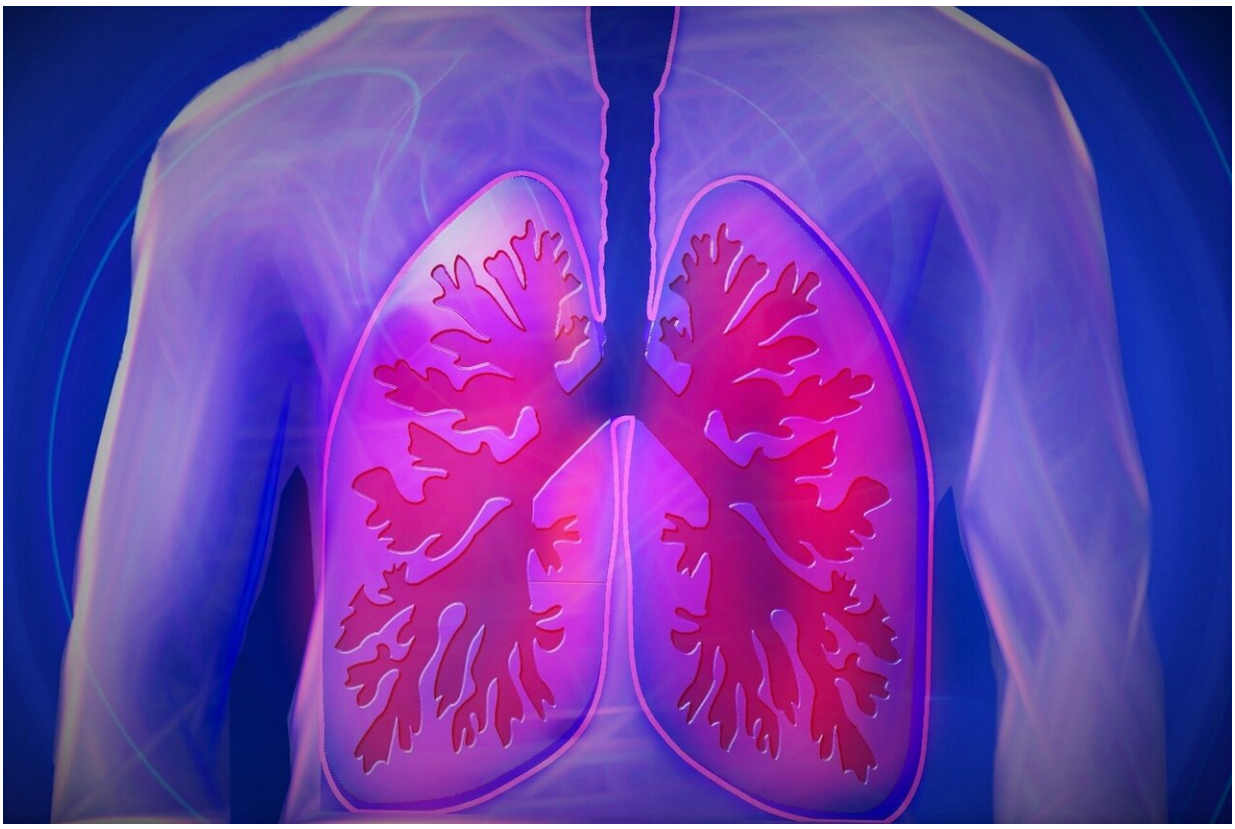

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University of Maryland School of Medicine (UMSOM) researchers found that lung transplant recipients who had early signs of organ

rejection could increase their chances of survival by using an inhaled form of the immunosuppression drug cyclosporine. This is the first randomized, controlled study to demonstrate increased survival and improved lung function using an investigational form of cyclosporine called liposomal cyclosporine, which can be inhaled. It is used in combination with an investigational nebulizer to deliver the drug to the lungs.

The researchers detail the results of a small, single-center clinical trial, conducted at the University of Maryland Medical Center (UMMC), in the journal *ERJ Open Research*.

"This drug may be a significant alternative that could improve the prognosis of lung transplant patients," 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 UMMC and lead author of the study. "While lung transplantation holds the promise of extending the lives of people with debilitating lung disease, chronic rejection, with its resulting decline in function, can wipe out that hope. Patients are often as sick as they were before the transplant. Once that happens, the options often come down to another lung transplant, or death."

Cyclosporine is traditionally given orally in pill form as part of the post-lung transplant standard-of-care regimen, one of several anti-rejection medications transplant recipients must take for the rest of their lives to prevent chronic organ rejection. Despite these measures, the immune system often succeeds in attacking the transplanted organ, with the result that nearly half of lung transplant recipients develop a life-threatening inflammatory condition called bronchiolitis obliterans syndrome (BOS) within five years of getting their transplant. It is the leading cause of post-lung transplant death; there is no proven treatment.

For this study, 21 lung transplant patients in the early stages of BOS were followed for 48 months. All patients were given conventional oral immunosuppressants, including tacrolimus, mycophenolate mofetil and prednisone; 11 were randomly selected to also receive the inhaled cyclosporine twice daily for 24 weeks. In this Phase 2B trial, designed to determine efficacy and safety, cyclosporine in a liposomal or bubbly form was tailored for fast and targeted drug aerosol delivery through a high-performance investigational nebulizer, the eFlow Nebulizer System (PARI Pharma GmbH).

The researchers found improved lung function in patients who received the inhaled liposomal cyclosporine without any additional toxicities, such as cough, shortness of breath and pharyngeal soreness. At 48 weeks post-transplant, progression-free survival was 82 percent for the treatment group versus 50 percent for the standard-of-care group. BOS grade significantly worsened for only 18 percent in the treatment group versus 60 percent in the control group. Lung function measures of forced expiratory volume and forced vital capacity stabilized in the treatment group but worsened with the controls. Most importantly, the median survival for those who received the inhaled cyclosporine was 4.1 years compared to 2.9 years for those who did not receive the added therapy. This study underscores that direct application of the medication to the lungs by inhalation may enhance the benefits while reducing the side effects of oral ingestion.

"We can get higher concentrations of the drug to the lungs through inhalation, compared to what we might get just by giving it by mouth," said Bartley P. Griffith, MD, the Thomas E. and Alice Marie Hales Distinguished Professor in Transplant Surgery at UMSOM, director of the Cardiac and Lung Transplant Program at UMMC and study co-author. "We are very pleased that we may be able to see this long-term idea realized in many more patients. We are offering both lung transplantation and hope."

Dr. Griffith and Dr. Iacono began investigating an inhaled form of cyclosporine back in the early-1990s, testing various drug formulations and aerosolized delivery systems, producing a mix of benefits and shortcomings. Their earlier attempts with a powdery form of cyclosporine, dissolved in propylene glycol and ethanol, showed the potential for increased survival, but also caused side effects such as persistent cough, pharyngeal soreness and other symptoms, limiting the drug's usefulness.

"The results of this study stand as a tribute to the many years of research it sometimes takes to develop a bright idea into a patient benefit," 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. "The results are promising, and so we look forward to the next phase: a larger trial to confirm both these benefits and the lack of additional side effects from the inhaled drug."

Based on the results of this investigation, patient enrollment in a global Phase 3 trial is underway.

More information: Aldo Iacono et al, A randomised single-centre trial of inhaled liposomal cyclosporine for bronchiolitis obliterans syndrome post-lung transplantation, *ERJ Open Research* (2019). DOI: 10.1183/23120541.00167-2019