Editorial

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Although the field of lung transplantation (LT) has evolved significantly in the past decades, there is an urgent need for the development of more effective strategies to improve graft and patient outcomes. The median 6.7-year post-transplant survival represents one of the lowest among solid organs and is limited primarily by allograft failure due to chronic lung allograft rejection (CLAD).

Thus, CLAD is one of the most important complications after lung transplantation, occurring in up to 50% of recipients within five years post-transplant. A number of distinctive features might explain this high prevalence: a large total surface area of vascular endothelium, constant exposure to environmental antigens, and an abundance of lymphoid tissue patrolled by a robust innate immune system.

CLAD is characterized by a persistent and mostly progressive fall in forced expiratory volume in one second (FEV_1) of > 20% compared with the postoperative best FEV_1 and is believed to be the consequence of chronic rejection. A consensus document from the International Society for Heart and Lung Transplantation identified different phenotypes of CLAD based on pulmonary lung function tests and chest imaging: bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), and a mixed BOS-RAS phenotype. The development of CLAD is likely multifactorial and related to the complex interaction of immune and non-immune factors.

Treatment options for CLAD are scarce. In this context, the community efforts have focused on understanding risk factors and looking for biomarkers to identify patients with higher risk of developing CLAD, two paramount strategies to promote preventive strategies and avoid lung function decline.

In the field of biomarkers, Ussetti et al. present an interesting study focusing on already available tools, such as eosinophil and lymphocyte counts, to identify patients at risk for CLAD. This paper studies in detail two different options of "everyday" biomarkers that have the advantage of being universally available at a very reasonable cost.

Advances in our understanding of the mechanisms driving lung allograft rejection have highlighted the relevance of intermittent or

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persistent inflammatory injuries to the graft. These occur in the context of complications such as primary graft dysfunction (which happens in 25% of lung transplant recipients), acute cellular rejection (with a prevalence between 30-50% during the first year), antibody-mediated rejection, presence of donor-specific antibodies, gastroesophageal reflux disease (GERD) or infections (bacterial, viral or fungal, and including colonization).

The importance of GERD as a risk factor for CLAD is highlighted by Izquierdo-Cuervo et al., with a review of diagnostic and therapeutic options. The need for standardized protocols is emphasized, as the LT community debates on how aggressively we should address this complication as a means of preventing CLAD.

Focusing on infections, new strategies include the use of bacteriophages to treat multidrug-resistant organisms. Berastegui-Garcia et al. summarize the data available and describe their center experience. Furthermore, Monforte et al. review the strategies available to monitor cytomegalovirus (CMV)-specific cellular immune response and their use after LT.

Promising future strategies include targeted delivery of lung-specific therapeutics using *ex vivo* lung perfusion, novel anti-inflammatory approaches (i.e., interleukin [IL]-6 signaling blockade), application of cell-based therapies (i.e., MSCs), harnessing of the regulatory potential of lung-specific memory T-cell populations, and tolerance induction. The ongoing development of advanced therapies in LT provides hope for a better future for lung transplant recipients.

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