

Immunological Insights Inform ILD & Transplant Outcomes

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Interstitial lung diseases (ILDs) present a complex challenge, often progressing to end-stage lung disease requiring transplantation. Post-transplant, chronic lung allograft dysfunction (CLAD) remains a significant barrier to long-term survival. Understanding the immunological underpinnings of both ILD progression and allograft rejection is critical for improving patient outcomes.

KEY TAKEAWAYS

- ° The Pivot: Specific immune cell subsets and cytokine profiles are implicated in ILD progression and CLAD development.
- ° The Data: Elevated levels of specific pro-fibrotic cytokines correlate with accelerated ILD progression (e.g., HR 1.85, 95% CI 1.32-2.59, $p=0.001$).
- ° The Action: Immunomodulatory strategies targeting identified pathways may offer therapeutic avenues for ILD and post-transplant care.

The progression of interstitial lung diseases (ILDs) is characterised by chronic inflammation and fibrosis, leading to irreversible lung damage. While the exact triggers vary across ILD subtypes, aberrant immune responses are consistently implicated. For instance, in idiopathic pulmonary fibrosis (IPF), dysregulated epithelial-mesenchymal transition is driven, in part, by pro-fibrotic cytokines and immune cell interactions.¹ Similarly, connective tissue disease-associated ILDs (CTD-ILDs) exhibit distinct immunological signatures, including autoantibody profiles and specific T-cell subsets, that correlate with disease activity and progression.² The prevalence of ILDs is estimated to be between 10 and 60 cases per 100,000 people globally, with IPF being the most common and severe form. These diseases significantly impair quality of life and are associated with high mortality rates, underscoring the urgent need for improved diagnostic and therapeutic strategies informed by a deeper understanding of their immunological underpinnings.

Lung transplantation offers a life-saving option for patients with end-stage ILD. However, long-term survival is frequently limited by chronic lung allograft dysfunction (CLAD), a broad term encompassing bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). CLAD is primarily an immunological process, driven by both alloimmune and auto-immune mechanisms.³ The complexity arises from the interplay between recipient immune responses to donor antigens and potential de novo autoimmunity triggered by the transplant itself.⁴ CLAD affects approximately 50% of lung transplant recipients within 5 years post-transplant, representing the leading cause of late mortality. Understanding the immunological drivers of CLAD is critical for developing effective prevention and treatment strategies.

Immunological Insights from ATS 2026

Recent presentations at ATS 2026 highlighted several immunological pathways and biomarkers relevant to both ILD progression and transplant outcomes. One area of focus was the role of specific T-cell subsets. Data indicated that an increased proportion of circulating Th17 cells and elevated levels of IL-17 in bronchoalveolar lavage fluid (BALF) were associated with accelerated decline in forced vital capacity (FVC) in a cohort of patients with progressive fibrosing ILD (N=210).⁵ The hazard ratio for FVC decline exceeding 10% annually was 1.85 (95% CI 1.32-2.59, P=0.001) in patients with high Th17 cell counts compared to those with lower counts.⁵ This suggests a potential pathogenic role for the Th17 axis in ILD fibrosis. The study population included patients with various progressive fibrosing ILD subtypes, such as IPF, CTD-ILD, and unclassifiable ILD, all demonstrating a progressive decline in lung function despite standard therapy. Th17 cells produce IL-17, a cytokine known to promote inflammation, neutrophil recruitment, and fibroblast activation, thereby contributing to fibrotic processes.

In the context of lung transplantation, research presented on immune monitoring strategies demonstrated the utility of donor-specific antibody (DSA) detection in predicting CLAD. A study involving 450 lung transplant recipients showed that the presence of de novo DSA (dnDSA) post-transplant was associated with a significantly higher incidence of CLAD at 5 years (42% vs. 18% in dnDSA-negative patients, $p<0.001$).⁶ Furthermore, specific HLA class II dnDSAs, particularly against DQ antigens, were identified as having a stronger association with restrictive allograft syndrome (RAS) than with bronchiolitis obliterans syndrome (BOS).⁶ This stratification of DSA risk by HLA specificity provides a more nuanced understanding of CLAD phenotypes. The study employed single-antigen bead assays for DSA detection and followed recipients prospectively for CLAD development, diagnosed according to ISHLT criteria.

Another area of investigation involved the role of innate immune cells. Macrophages, particularly those with a pro-fibrotic M2 phenotype, were shown to accumulate in fibrotic lung tissue of ILD patients and contribute to extracellular matrix deposition.⁷ Targeting macrophage activation pathways, such as through inhibition of colony-stimulating factor 1 receptor (CSF1R), demonstrated reduced fibrosis in preclinical models of ILD.⁷ In the transplant setting, dysregulation of regulatory T cells (Tregs) was linked to increased susceptibility to chronic rejection. A study found that a lower ratio of Tregs to conventional T cells in peripheral blood at 1 year post-transplant correlated with a higher risk of CLAD development over the subsequent 4 years (HR 2.10, 95% CI 1.55-2.85, $p<0.001$).⁸ Tregs play a crucial role in maintaining immune tolerance, and their quantitative or functional impairment can lead to unchecked alloimmune responses.

These immunological insights underscore the complex interplay of cellular and humoral immunity in both ILD pathogenesis and allograft rejection. While the data presented offer compelling correlations and mechanistic hypotheses, many studies were observational or preclinical. Larger prospective trials are required to validate these biomarkers and evaluate the efficacy of targeted immunomodulatory interventions in clinical practice. The heterogeneity of ILD and CLAD phenotypes also necessitates further research into personalised immunological profiling to guide therapeutic decisions. Limitations of the presented data include the single-center nature of some studies and the need for external validation in diverse patient cohorts to ensure generalisability.

CLINICAL IMPLICATIONS

The consistent identification of specific immune cell subsets and cytokine profiles across ILD progression and transplant rejection offers a clear direction for clinical practice. For the pulmonologist managing progressive fibrosing ILD, the data on Th17 cells and IL-17 levels, while still requiring validation in larger cohorts, suggest potential biomarkers for identifying patients at higher risk of rapid decline. This could inform earlier consideration of anti-fibrotic therapies or enrolment in trials for novel immunomodulators. The current reliance on FVC decline alone as a prognostic marker may be augmented by these immunological insights, allowing for more proactive management.

For transplant physicians, the detailed stratification of DSA risk, particularly the distinction between HLA class I and II and their association with specific CLAD phenotypes, refines our understanding of post-transplant immune surveillance. This precision in risk assessment could lead to more targeted immunosuppression strategies, moving beyond broad-spectrum approaches. For example, patients with high-risk DQ dnDSAs might benefit from intensified desensitisation protocols or novel anti-humoral therapies, potentially reducing the incidence of RAS. The industry will undoubtedly respond with diagnostic platforms offering more granular HLA antibody analysis, and pharmaceutical companies may focus on developing agents that specifically modulate these identified pathways, rather than broad immunosuppressants with their associated side effects. Ultimately, these immunological insights point towards a future of personalised medicine in ILD and lung transplantation. Patients stand to benefit from earlier identification of disease progression, more precise risk stratification for rejection, and potentially, therapies that specifically target the immunological drivers of their disease rather than broadly suppressing the immune system. The challenge will be to translate these complex immunological findings into accessible, actionable clinical tools that can be implemented in routine practice, ensuring that the benefits reach beyond specialist centres.

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