ISHLT June 2024 | Pulmonology
JOURNAL WATCH

Umil Shah, MD, DNB
KIMS Heart and Lung Transplant Institute | Hyderabad, India

Mrinalini Venkata Subramani, MD
Junior Editor, Pulmonology

ISHLT.ORG

Effect of once-per-day tacrolimus versus twice-per-day ciclosporin on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD):Multicentre RCT

Dellgren G, Lung T, Raivio P, et al. Lancet Respir Med 2024;12(1):34-44. DOI: 10.1016/S2213-2600(23)00293-X

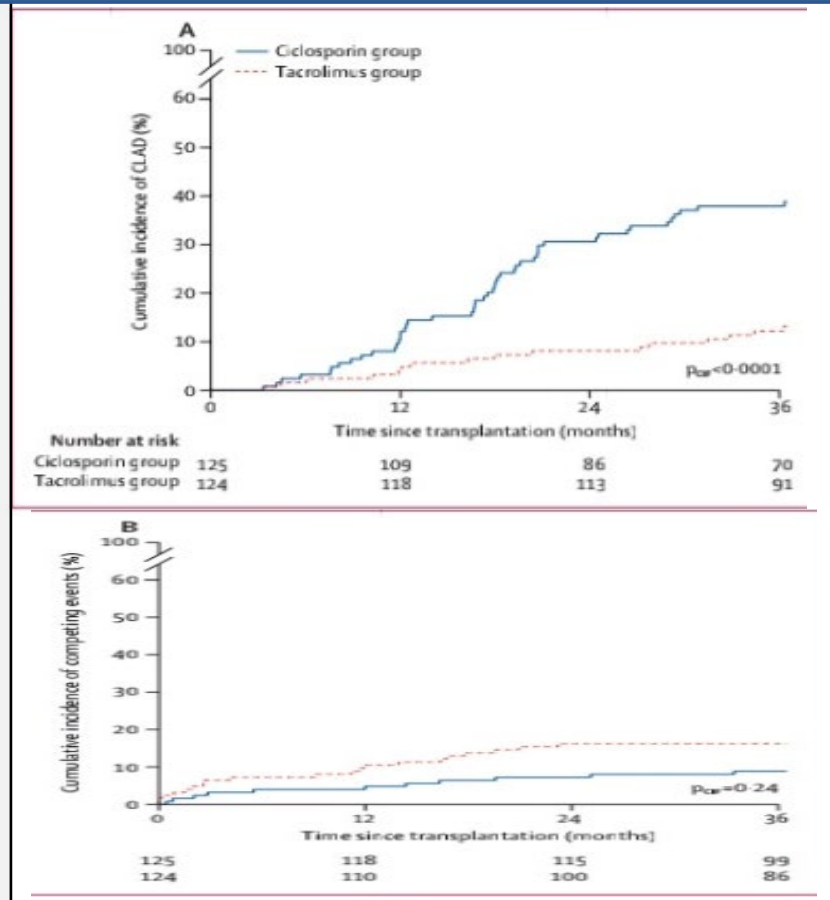
Study Highlights

Objective: Evidence is low regarding the choice of calcineurin inhibitor for immunosuppression after lung transplantation. Aim is to compare the use of tacrolimus once per day with ciclosporin twice per day according to the current definition of chronic lung allograft dysfunction (CLAD) after lung transplantation.

Methods: Patients aged 18–70 years who were scheduled to undergo double lung transplantation were randomly allocated (1:1) to receive either oral ciclosporin (2–3 mg/kg before transplantation and 3 mg/kg [twice per day] from postoperative day 1) or oral tacrolimus (0·05–0·1 mg/kg before transplantation and 0·1–0·2 mg/kg from postoperative day 1. The primary endpoint was CLAD at 36 months post transplantation, determined by repeated lung function tests and adjudicated by an independent committee.

Results:249 patients underwent double lung transplantation and received at least one dose of study drug, and were thus included in the modified intention to treat population(mITT): 125 (50%) in the ciclosporin group and 124 (50%) in the tacrolimus group. In the mITT population, CLAD occurred in 48 patients (cumulative incidence 39% [95% CI 31–48]) in the ciclosporin group and 16 patients (13% [8–21]) in the tacrolimus group at 36 months post transplantation (hazard ratio [HR] 0·28 [95% CI 0·15–0·52], log-rank p<0·0001). CLAD population (those in the mITT population who also had at least one post-baseline lung function test allowing assessment of CLAD), allograft survival was significantly better in the tacrolimus group (HR 0·49 [95% CI 0·26–0·91], log-rank p=0·021)

Conclusions: Use of tacrolimus once per day significantly reduced the incidence of CLAD compared with use of ciclosporin twice per day. These findings support the use of tacrolimus as the first choice of calcineurin inhibitor after lung transplantation.



- **Figure 3:** Competing-risks analysis of CLAD, death and re-transplantation in mITT Legend(A):Cumulative incidence of CLAD with death and re-transplant as competing events.
- **Legend (B):** Cumulative incidence of competing events i.e death or re-transplantation with CLAD as a primary event.
- P value from Fine and Gray's test of difference between two cumulative incidence functions.

Reviewer's Comments

- The pragmatic study design across 5 European centers evaluates real-world practices and increases generalizability.
- This RCT adds further data and increases the level of evidence for using tacrolimus as the calcineurin inhibitor of choice after lung transplantation.
- The findings show a clear difference in the incidence of CLAD, acute rejection, and the combined endpoint of treated acute rejection, CLAD, graft survival, and patient survival, in tacrolimus vs ciclosporin group.
- The several sub studies under Scan CLAD trial will provide urgently needed answers on post transplant comorbidties.

Limitations

- The open-label , non blinded nature of the study design can introduce bias.
- Non-blinded nature of the trial could impact patient-adherence and clinical management of the patient.
- Long term follow up increases the risk of patient drop out and changes in clinical practices.
- There are limitations to current CLAD definition and classification of phenotypes .
- Secondary outcomes analysis (including CLAD phenotype, donor-specific antibodies, kidney function,) are awaited.

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Bronwyn Small, MD
Ohio State University, Wexner Medical Center | Columbus, OH USA

Mrinalini Venkata Subramani, MD
Junior Editor, Pulmonology
ISHLT.ORG

Impact of Transient and Persistent Donor-Specific Antibodies in Lung Transplantation

Auner S, Hillebrand C, Boehm PM, et al. Transpl Int 08 May 2024. DOI: 10.3389/ti.2024.12774

Study Highlights

Objective: Investigate the clinical significance of transient and persistent de novo donor-specific antibodies (dnDSAs), and their impact outcomes after lung transplant (LuTx).

Methods:

- Retrospective single-center review at the Medical University of Vienna from February 2016 to March 2021. All adults with dnDSA after primary transplant (retransplant and multi-organ excluded). Antibodies with an MFI>1,000 which were not detected or were below threshold before transplant classified as dnDSA. Transient dnDSAs: detected for < 6 months, Persistent dnDSAs: Detected for > 6 months post-transplant. DSAs screened at 2 weeks, 1-,2-,3,6- and 12-months post-transplant and in cases of clinical deterioration.

Results:

- n = 405 LuTx recipients, 205 developed dnDSA over 3.44 years. Transient dsDSA = 167 (81%), Persistent dnDSA = 38 (19%)
- HLA A, B, DQ, and DR dsDSA were more commonly persistent (p<0.001).Persistent HLA-DQ antibodies were associated with a higher incidence of AMR and CLAD and worse overall survival (all p<0.05). Persistent dnDSA against HLA-A was associated with increased risk of AMR but not CLAD
- AMR occurred in 22 LuTx (11%),and was more common in those with persistent DSA (24%),and was associated with decreased survival (p<0.001).Univariate and multivariate cox regression showed AMR as the only independent risk factors for impaired survival (p<0.01) and for CLAD (p = 0.03)

Conclusions: Persistent DSA is associated with increased risk of AMR and decreases CLAD free survival.

Figure 2 Kaplan-Meier curve showing AMR-free survival for patients with transient and persistent DSA (p =0.04)

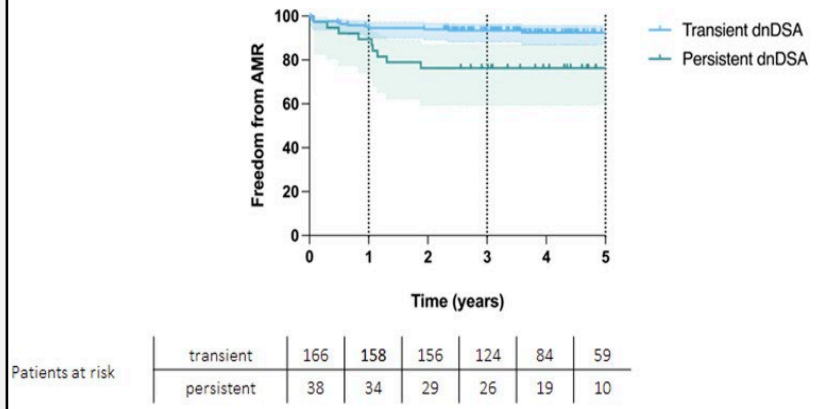
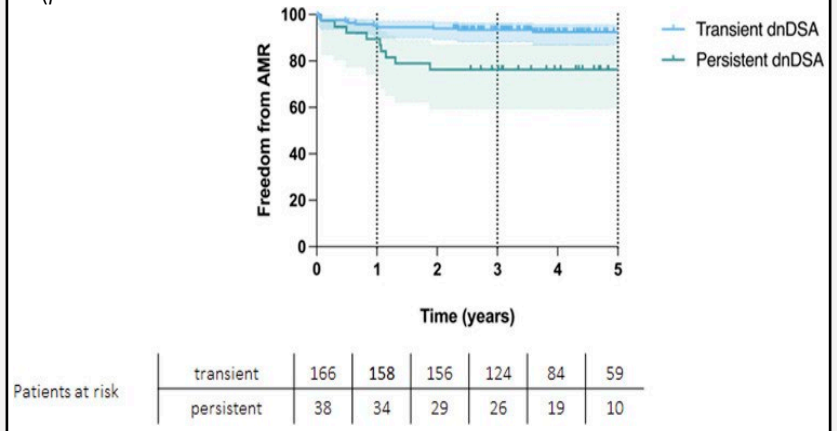


Figure 3 Kaplan-Meier curve showing CLAD-free survival for patients with transient and persistent DSAs (*p* = 0.004



Reviewer's Comments

- This study demonstrates the significance of persistent DSA in decreased AMR- and CLAD-free survival.
- Timing and selection for pre-emptive treatment of transient/persistent dnDNA remains unclear with this data, despite their potential deleterious effects.
- AMR diagnosis was a poor prognostic factor for overall survival– thus its appropriate (and timely) diagnosis and treatment remain critical with transient/persistent dnDSA.
- dnDSA persistence supports sequential antibody monitoring and increased vigilance for development of AMR.
- These results also support the need for improved diagnostic definitions of AMR, potentially using molecular diagnostics (e.g. cfDNA)

Limitations

- Single-center study, retrospective in nature.
- Varied protocols of induction therapy, desensitization and AMR protocols were in place over duration of the study that makes generalizability difficult.
- Definition of transient versus persistent dsDNA is not well established but reported based on clinical experience and could vary center to center.
- No explicit description of diagnostic criteria for AMR, but assume to have followed ISHLT consensus criteria.
- There is well recognized pitfalls in the ISHLT AMR criteria with regards to C4d staining in lungs.

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Sravanthi Nandavaram, MD, FCCP
Massachusetts General Hospital | Boston, MA USA

Mrinalini Venkata Subramani, MD
Junior Editor, Pulmonology
ISHLT.ORG

Ventilatory capacity in CLAD is driven by dysfunctional airway structure

Kerckhof P, Ambrocio GPL, Beeckmans H, et al. eBioMedicine Mar 2024;101:105030. DOI: 10.1016/j.ebiom.2024.105030

Study Highlights

Objective: CLAD affects up to 50% of patients within 5 years of transplantation. CLAD Phenotypes include BOS, RAS, Mixed, undefined. It is unclear how the airway morphology and airway obstruction affect the regional ventilatory capacity within the lung among the CLAD phenotypes.

Methods:

- Airway morphometric analysis was performed via ex vivo whole lung microCT and tissue core microCT scans to assess the airway remodeling and its effect on alveolar ventilation.18 explanted lungs were studied - 6 control, 6 BOS, 3 mixed and 3 RAS.

Results:

- Whole lung µCT in BOS showed mostly radiologically normal lung parenchyma with occasional interlobular septal thickening and discrete areas of peripleural attenuation. In RAS, it showed a variable degree of parenchymal and peri-pleural fibrosis with adjacent traction bronchiectasis of the larger airways.
- Obstructive lesions were more noted in the proximal bronchioles in BOS (76%), while in RAS distal bronchioles (22%) were severely affected, often embedded in fibrosis. In mixed phenotype, both proximal and distal airways (84%) were affected.
- The main determinant factor for obstruction is airway diameter rather than airway generation. Morphologically obstructive lesions can be bronchiolar webs, mucus plug, obliterative bronchiolitis and histologically mainly caused by lymphocytic inflammation of the airway wall or fibrotic remodeling, constrictive bronchiolitis

Conclusions: Pathophysiological processes appear to overlap among CLAD phenotypes. The extent and the type of airway morphologic changes explain the pulmonary function parameters in CLAD.

Figure 2 Whole lung µCT scans and reconstructed airways. (a, b) Lung parenchyma and total airway tree of a control (left lung), (c, d) BOS (right lung), (e, f) Mixed (Left lung) and (g, h) RAS (Left lung) lung.

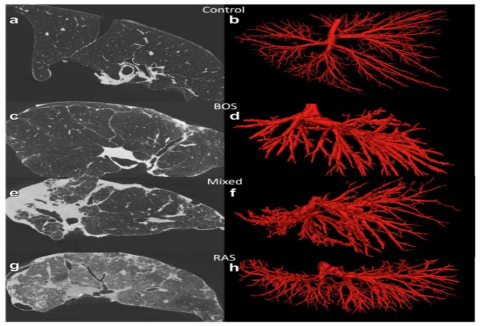


Fig. 2: **Whole lung µCT scans and reconstructed airways**. (a, b) Lung parenchyma and total airway tree of a control (left lung), (c, d) BOS (right lung), (e, f) Mixed (Left lung) and (g, h) RAS (Left lung) lung.

Figure 3 Number of obstructions. (a) Number of non-occluded (open) airway segments per airway generation. Dunnet post-hoc test showed significant differences between BOS and control ($p < 0.05*$, $p < 0.01**$) and between Mixed and control ($p < 0.05^{\S}$) in some generations, as indicated in the figure.

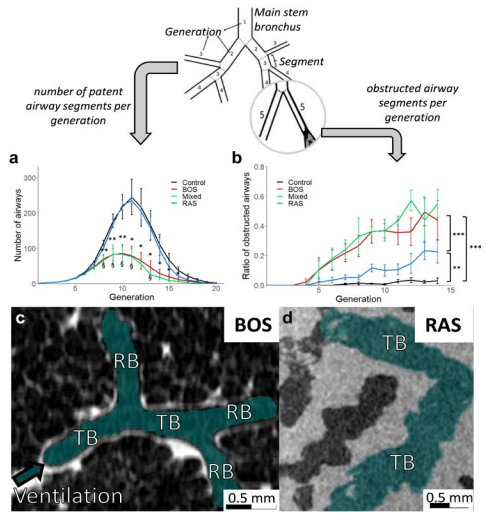
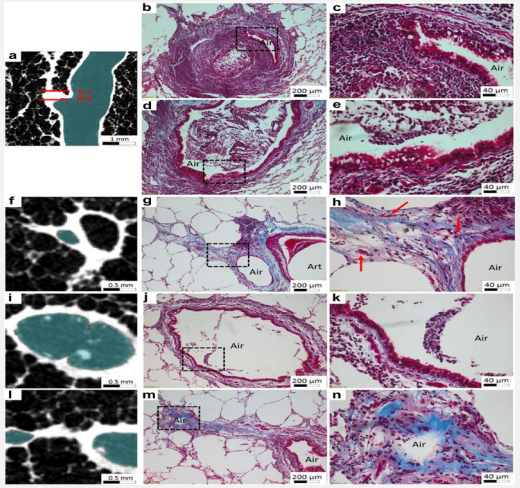


Figure 9 Masson's trichrome staining on some of the lesions of Fig. 8. (a–e) Lymphocytic inflammation with neo-angiogenesis. Fig. 9f where the lumen has disappeared. Red arrows show smooth muscle, indicating that this is an occluded bronchiole. Lymphocytic inflammation is seen on top of the airway in Fig. 9g. (i–k) Example of a web: fibrinous-mucinous matrix filled with various immune cells. (l–n) Constrictive bronchiolitis with collagen deposition and lack of airway epithelium



Reviewer's Comments

- Both CLAD and RAS have overlapping features. This research highlights the importance of various histologic features of CLAD that provides insight into role of mucus stasis in CLAD.
- Highlights the importance of more research to understand regional ventilatory impairment in CLAD

Limitations

- Study sample size is small.
- Study performed on static explanted lungs, hence might not provide the same ventilatory capacity insight as in dynamic in vivo airways.

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Sravanthi Nandavaram, MD, FCCP
Massachusetts General Hospital | Boston, MA USA

Mrinalini Venkata Subramani, MD
Junior Editor, Pulmonology
ISHLT.ORG

Spectrum of chronic lung allograft dysfunction pathology in human lung transplantation

Renaud-Picard B, Berra G, Hwang D, et al. J Heart Lung 22 Apr 2024. DOI: 10.1016/j.healun.2024.04.002

Study Highlights

Objective: Chronic Lung Allograft Dysfunction (CLAD), which includes two main phenotypes: bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), with possible overlap. We aimed to detail and quantify pathological features of these CLAD sub-types.

Methods: Peripheral and central paraffin-embedded explanted lung samples were obtained from 20 consecutive patients undergoing a second LTx for CLAD, from 3 lobes. Thirteen lung samples, collected from non-transplant lobectomies or donor lungs, were used as controls.

- Blinded semi-quantitative grading was performed to assess airway fibrotic changes, parenchymal and pleural fibrosis, as well as epithelial and vascular abnormalities.
- The following histological features were evaluated peri-airway fibrosis (PAF), bronchiolitis obliterans (BO), and pleural fibrosis (PLF),Parenchymal fibrosis (PF), Epithelial changes: epithelial hyperplasia (EH) and epithelial flattening (EF), Peri-airway inflammation ,presence of a lymphoid aggregate (LA), Vascular fibrosis, endothelialitis

Results: PAF and BO were significantly higher in both BOS (p=0.002 and p<0.0001, respectively) and RAS (p=0.0008 and p<0.0001, respectively) compared to control samples. Lung PF scores were significantly higher in RAS compared to controls (p<0.0001) and BOS (p=0.003) and higher in BOS compared to controls (p=0.02)

- EH and EF scores were significantly higher in BOS (p=0.003 and p<0.0001, respectively), and RAS (p=0.0003 and p<0.0001 respectively) compared to controls, without any significant difference between CLAD phenotypes.
- There was also a significant positive correlation between peri-airway inflammation and PAF, BO, EH (p<0.0001 for all). Airway fibrosis-related parameters (PAF and BO) were also significantly related to epithelial hyperplasia (p<0.0001 for both)
- The frequency of CCSP+ club cells among all epithelial cells was higher in the controls [11.4% (0.7–29.3)] compared to BOS or RAS [1.3% (0.4–3.8) and 0.4% (0.21-14.9) respectively (p=0.07)], without any difference between the two CLAD phenotypes

Conclusions: Study highlights the inter- and intra-patient heterogeneity of injuries affecting the different compartments of CLAD lung allografts and confirms a significant histological overlap between well-defined clinical BOS and RAS. This may suggest a common pathophysiology, the extent and location of histological changes may determine the clinical phenotype.

Figure 2 Histological parameters used for the grading system assessing the pathological spectrum in chronic lung allograft dysfunction

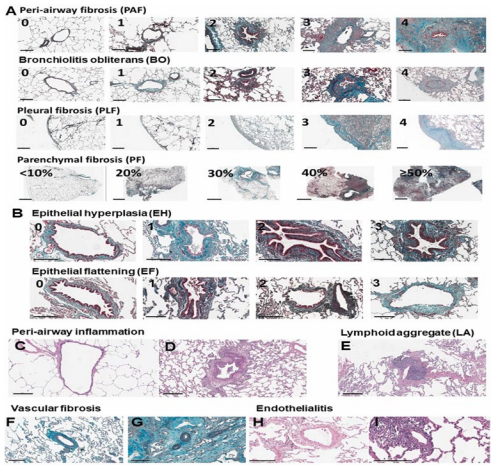
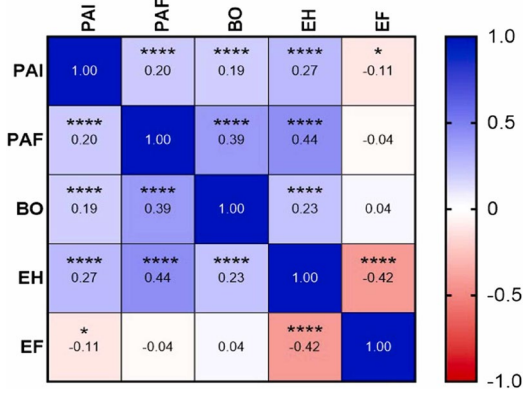


Figure 4 Significant correlation between peri-airway inflammation, airway fibrosis-related parameters and epithelial gradings. Significant positive correlation between peri-airway inflammation, peri-airway fibrosis (p<0.0001), bronchiolitis obliterans (p<0.0001) and hyperplasia (p<0.0001);significant negative correlationbetween peri-airway inflammation and epithelial flattening (p=0.01).



Reviewer's Comments

- The strengths of this study include systematic and standardized phenotyping of CLAD patients at the time of lung explantation and the inclusion of control group. The semi-quantitative histological grading score showed a generally high inter-reader reliability and may be useful for future CLAD pathological assessments.
- The heterogeneity in the distribution of CLAD with large areas of lung sparing warrants further research to identify etiology of progression to CLAD.
- This work highlights the importance of epithelial injury in development of CLAD. The observed negative correlation between BO and the frequency of club cells within the epithelium of the small airways, may be part of mechanisms leading to CLAD.

Limitations

- This was a descriptive, retrospective, single-center study.
- In some samples, the histological assessment may have been over- or underestimated for certain parameters, for instance with epithelial hyperplasia and flattening, where a tangential cut could have been made across the airway.
- Most of the recipients were quite young and had cystic fibrosis, so findings may not be entirely representative of an older population