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Safety and Clinical Effectiveness of Anti-Thymocyte Globulin in Rapidly Progressive Chronic Lung Allograft Dysfunction: A Retrospective Cohort Study

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ABSTRACT

Background: Chronic lung allograft dysfunction remains the leading barrier to long-term graft survival after lung transplantation. Therapeutic options are limited once lung function begins to decline rapidly, and the role of anti-thymocyte globulin in this setting remains incompletely defined. This study evaluated the clinical effectiveness and safety of anti-thymocyte globulin in patients with rapidly progressive chronic lung allograft dysfunction. **Methods:** We performed a retrospective single-center cohort study of adult lung transplant recipients diagnosed with chronic lung allograft dysfunction between 2013 and 2023. Rapidly progressive chronic lung allograft dysfunction was defined a priori as a decline in FEV_1 exceeding 100 mL/month over the 3-month period preceding treatment or index-date assessment, confirmed by at least 3 spirometric measurements. Patients treated with anti-thymocyte globulin for progressive chronic lung allograft dysfunction were compared with contemporaneous patients with rapidly progressive chronic lung allograft dysfunction who did not receive anti-thymocyte globulin. The primary effectiveness endpoint was change in the rate of FEV_1 decline during the 6 months before and after anti-thymocyte globulin administration. Secondary endpoints included partial response, complete response, post-chronic lung allograft dysfunction graft survival, and treatment-related safety outcomes. Propensity-score matching was used for survival comparison between treated and untreated groups. **Results:** Of 187 lung transplant recipients reviewed, 168 developed chronic lung allograft dysfunction and 112 met criteria for rapidly progressive disease. Among these, 64 received anti-thymocyte globulin and 48 did not. After exclusion for inadequate spirometric follow-up, 58 anti-thymocyte globulin-treated patients were included in the effectiveness analysis. The mean pre-anti-thymocyte globulin FEV_1 slope was -1.78 mL/day, improving to -1.49 mL/day after treatment (mean difference 0.29 mL/day, 95% CI 0.01–0.57, p=0.04). A partial response was observed in 69.0%, while a complete response was observed in 8.6%. In propensity-matched analysis (40 pairs), median graft survival was 28.4 months in the anti-thymocyte globulin group versus 19.2 months in the control group. The hazard ratio for graft failure was 0.71 (95% CI 0.46–1.09, p=0.12), which did not reach statistical significance. Infectious complications within 6 months of anti-thymocyte globulin occurred in 27.6%, with bacterial pneumonia as the most common event. **Conclusions:** In patients with rapidly progressive chronic lung allograft dysfunction, anti-thymocyte globulin was associated with modest attenuation of FEV_1 decline. However, no statistically significant survival benefit was detected. The substantial burden of infectious complications (27.6%) and hematologic toxicity (36.2%) underscores the need for careful patient selection. These findings are hypothesis-generating rather than definitive. Prospective randomized trials are needed to determine whether any survival benefit exists and to establish the optimal risk-benefit profile for this therapy.

KEYWORDS: lung transplantation; chronic lung allograft dysfunction; anti-thymocyte globulin; bronchiolitis obliterans syndrome; restrictive allograft syndrome; graft survival; spirometry; infection

1 Introduction

Lung transplantation remains the definitive treatment for selected patients with end-stage pulmonary disease, yet long-term outcomes continue to be constrained by chronic lung allograft dysfunction (CLAD) [1–3]. CLAD is a progressive clinical syndrome characterized by sustained deterioration in allograft function after exclusion of reversible causes [3]. Its major phenotypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), differ in physiology and radiographic pattern but share an unfavorable impact on graft longevity and patient survival [3, 4]. Once CLAD becomes clinically apparent, treatment is often empiric, heterogeneous across centers, and frequently unsatisfactory [5, 6].

The subgroup of patients with rapidly progressive CLAD represents a particularly high-risk population. In these patients, accelerated loss of FEV_1 may reflect ongoing alloimmune injury, irreversible small-airway fibrosis, mixed inflammatory and fibrotic remodeling, or a combination of these processes [5, 7]. From a clinical standpoint, rapid progression is important because it compresses the therapeutic window during which salvage treatment might still alter the course of disease. Stabilization of lung function, rather than recovery to prior baseline, may therefore represent a meaningful therapeutic goal in this setting [5, 6].

Anti-thymocyte globulin (ATG) has been used in lung transplantation as an induction agent and as treatment for steroid-refractory acute rejection [8, 9]. Its use in CLAD is less standardized and typically reserved for patients with progressive disease despite optimization of baseline immunosuppression and adjunctive therapies such as azithromycin or extracorporeal photopheresis [10–13]. Existing reports suggest that ATG may attenuate the rate of FEV_1 decline in some patients, but the magnitude, consistency, and clinical significance of that effect remain uncertain [14–16, 18]. Concerns also persist regarding infectious toxicity, hematologic adverse events, and longer-term immunosuppressive burden [15, 18, 19].

The present study was designed to evaluate the safety and clinical effectiveness of ATG specifically in rapidly progressive CLAD. By focusing on a subgroup with accelerated deterioration in lung function, this study sought to address a clinically important question not fully captured by broader CLAD cohorts [3–5]. We hypothesized that ATG would be associated with attenuation of FEV_1 decline in a subset of patients with rapidly progressive disease, but that this potential benefit would be offset by a substantial burden of treatment-related complications.

2 Materials and Methods

2.1 Study Design and Setting

This was a retrospective observational cohort study performed at *Vanderbilt University Medical Center*, a tertiary lung transplant center. Adult lung transplant recipients followed between *2013* and *2023* were screened for CLAD. The study was approved by the institutional review board of Vanderbilt University with waiver of informed consent due to the retrospective nature of the analysis.

2.2 Study Population

Eligible patients were adults aged 18 years or older who underwent single or bilateral lung transplantation and subsequently developed CLAD during the study period. CLAD diagnosis, stage, and phenotype were assigned retrospectively using contemporary International Society for Heart and Lung Transplantation criteria [3, 4]. Patients were further screened for rapidly progressive CLAD, defined as a decline in FEV_1 exceeding *100 mL/month* during the *3-month* interval preceding therapy initiation or index date, based on at least *3* spirometric measurements.

Patients were assigned to one of two groups. The *ATG cohort* included patients who received ATG specifically for rapidly progressive CLAD. The *non-ATG cohort* included patients with rapidly progressive CLAD managed without ATG during the same era. Exclusion criteria were age below 18 years, multiorgan transplantation, active untreated infection at the time of index assessment, biopsy-proven acute cellular rejection greater than A0 within *30* days before ATG, probable antibody-mediated rejection at the time of treatment, lack of sufficient spirometric data for slope analysis, receipt of ATG for indications other than CLAD, and retransplantation before evaluable follow-up.

2.3 Definition of Rapidly Progressive CLAD

Rapidly progressive CLAD was defined a priori to distinguish patients with clinically meaningful short-term decline from those with indolent disease. The primary definition used a loss of more than *100*

mL/month in FEV_1 over the pre-index interval. A sensitivity analysis was prespecified using an alternative threshold of *75 mL/month* to test robustness of findings. The index date for ATG-treated patients was the first day of ATG administration; for untreated controls, the index date was the date on which rapidly progressive CLAD criteria were first met.

2.4 ATG Exposure and Treatment Protocol

ATG was administered according to institutional practice. Rabbit ATG (Thymoglobulin, Sanofi) was preferred when clinically appropriate and was given over *4-5* days to a target cumulative dose of *5–7.5 mg/kg*. Equine ATG (Atgam, Pfizer) was reserved for selected patients based on prior exposure, intolerance, formulary availability, or physician discretion. Premedication typically included acetaminophen, antihistamine, and corticosteroid therapy. Patients underwent laboratory monitoring including complete blood counts and CD3 or lymphocyte counts during therapy. Antimicrobial prophylaxis followed institutional transplant protocols and included trimethoprim-sulfamethoxazole for PJP prophylaxis, valganciclovir for CMV prophylaxis when indicated, and antifungal prophylaxis for 3 months in high-risk patients.

2.5 Data Collection

Demographic, transplant-related, physiologic, immunologic, and treatment variables were abstracted from the electronic medical record. Baseline variables included age, sex, race/ethnicity, indication for transplantation, transplant type, post-transplant best FEV_1, time from transplant to CLAD onset, CLAD phenotype, CLAD stage at index date, donor-specific antibody status, absolute neutrophil count, absolute lymphocyte count, serum creatinine, prior acute rejection history, baseline maintenance immunosuppression, and concurrent azithromycin or extracorporeal photopheresis use. Among ATG-treated patients, ATG formulation, cumulative dose, duration of administration, and time from CLAD diagnosis to ATG were recorded.

2.6 Outcomes

The primary effectiveness outcome was change in the rate of FEV_1 decline before versus after ATG. For ATG-treated patients, all available FEV_1 values from the 6 months preceding and the 6 months following ATG administration were collected. Linear regression was used to estimate the slope of FEV_1 over time in each interval. A complete response was defined as conversion to a positive post-treatment FEV_1 slope. A partial response was defined as attenuation of the rate of decline by more than 20% relative to the pre-treatment slope. Patients not meeting either definition were classified as nonresponders.

For untreated controls included in matched analyses, FEV_1 slopes were similarly assessed over symmetrical pre-index and post-index intervals where data were available. A secondary functional endpoint was absolute change in FEV_1 at *3* and *6* months after index date.

The survival endpoint was graft survival, defined as time from rapidly progressive CLAD onset to death or retransplantation. Patients alive without retransplantation at last follow-up were censored on *December 31, 2023*.

Safety endpoints included infectious complications within 6 months after ATG, new-onset cytopenias, infusion-related adverse events, hospitalization attributable to treatment toxicity, need for premature discontinuation of therapy, and new malignancy during post-ATG follow-up. Infectious events required microbiologic, molecular, or antigen-based evidence together with clinician documentation supporting active infection rather than colonization.

2.7 Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median with interquartile range according to distribution. Categorical variables were summarized as counts and percentages. Between-group comparisons were performed with Student's t test or Wilcoxon rank-sum test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Within the ATG cohort, pre- and post-treatment FEV_1 slopes were compared using paired t-tests, and baseline variables associated with partial or complete response were explored using univariable logistic regression. Variables meeting a threshold of $p < 0.10$ in univariable analysis or judged clinically important a priori were entered into multivariable models.

Kaplan–Meier methods were used to estimate graft survival, and groups were compared using the log-rank test. Cox proportional hazards models were constructed to assess associations between baseline

covariates and post-CLAD graft survival. To reduce confounding in treated-versus-untreated comparisons, propensity scores were estimated using a logistic model incorporating age, transplant type, time from transplant to CLAD onset, best post-transplant FEV_1, CLAD phenotype, CLAD stage, and baseline rate of decline in FEV_1. Patients were matched 1:1 by nearest neighbor matching without replacement using a caliper of *0.2 standard deviations of the logit of the propensity score*. Covariate balance after matching was assessed using standardized mean differences. Statistical analyses were performed using *R* version *4.2.1* (R Foundation for Statistical Computing), and two-sided p values < 0.05 were considered statistically significant.

2.8 Limitations of Propensity Matching in Salvage Therapy Studies

Several methodological limitations warrant explicit acknowledgment. First, the small size of the untreated comparator group (n=48) limits the stability of propensity score estimation and the precision of hazard ratios derived from matched analyses. With only 48 untreated patients available for matching, the maximum number of matched pairs was 40, which provides limited statistical power to detect modest survival differences. Second, propensity matching can only balance measured confounders included in the logistic model. Unmeasured confounding—particularly regarding the clinical decision to administer ATG—cannot be addressed by this approach. In salvage therapy studies, clinicians typically reserve ATG for patients perceived to be deteriorating despite standard therapy, which may introduce confounding by indication that propensity methods cannot fully eliminate. Third, the small sample size precludes meaningful subgroup analyses by CLAD phenotype (BOS vs. RAS), which may have different responses to immunotherapy. Fourth, the retrospective design means that spirometric surveillance was not standardized across all patients, potentially introducing measurement bias. Given these limitations, the results of this study should be considered hypothesis-generating rather than definitive. All statistical comparisons were prespecified as exploratory.

For transparency, we report that the propensity model included the following baseline covariates: age, transplant type (single vs. bilateral), time from transplant to CLAD onset, best post-transplant FEV_1, CLAD phenotype (BOS/RAS/other), CLAD stage (1-4), and pre-index FEV_1 slope. Covariate balance after matching was assessed using standardized mean differences, with values <0.1 considered well-balanced. Despite these efforts, residual confounding remains possible.

3 Results

3.1 Cohort Assembly and Baseline Characteristics

During the study period, *187* lung transplant recipients were screened, of whom *168* developed CLAD. Among these, *112* satisfied criteria for rapidly progressive CLAD. A total of *64* patients received ATG for rapidly progressive CLAD and *48* met criteria for the non-ATG comparator group. After excluding patients with inadequate spirometric follow-up (n=6 in the ATG group, n=12 in the control group), *58* ATG-treated patients and *36* controls remained eligible for the primary effectiveness analysis. Propensity-matched survival cohorts included *40* treated and *40* untreated patients (1:1 matching from the 48 available controls). Cohort assembly is shown in Figure 1.

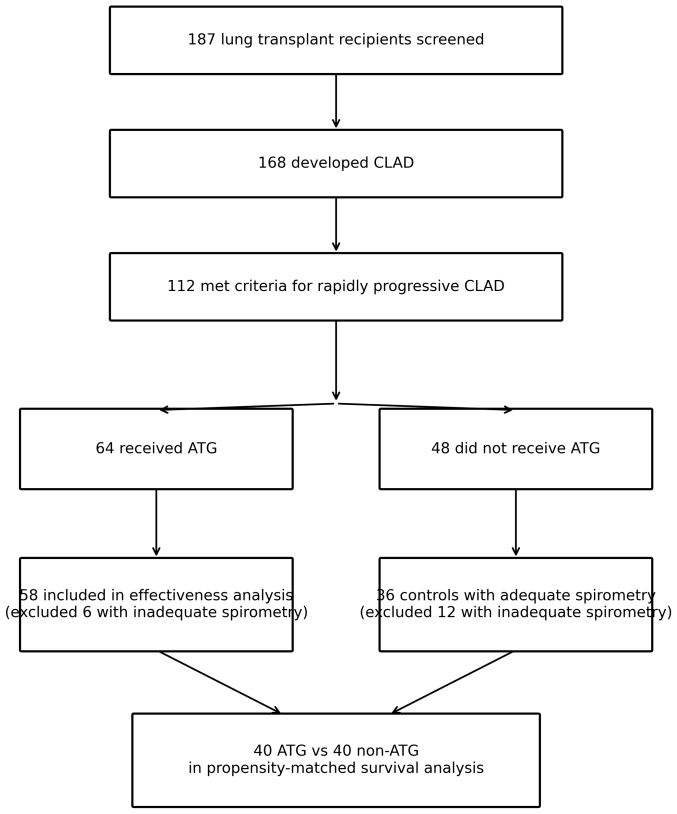

Figure 1. Cohort assembly of lung transplant recipients screened for CLAD, identification of rapidly progressive CLAD, application of inclusion and exclusion criteria, and derivation of ATG and non-ATG cohorts.

Baseline characteristics are summarized in Table 1. The mean age at transplantation was *55.3* years, *60.2%* were male, and the most common indications for transplant were interstitial lung disease (45.5%) and COPD (34.8%). Bilateral lung transplantation accounted for *83.9%* of the cohort. At the time of index-date assessment, *69.6%* had BOS, *23.2%* had RAS, and *7.1%* had mixed or unclassifiable phenotype. Most patients had stage *2* CLAD at the time rapidly progressive disease was identified. The mean best post-transplant FEV_1 was *2.41 L*, and the median time from transplant to CLAD onset was *41* months.

Table 1. Baseline demographic and clinical characteristics of patients with rapidly progressive CLAD, stratified by receipt of ATG.

Variable	Non-ATG (n=48)	ATG (n=64)	*p* value
Age at transplantation, years	56.0 ± 11.8	54.7 ± 12.3	0.58
Male sex, *n* (%)	29 (60.4)	38 (59.4)	0.91
Ethnicity (White/Black/Other)	39/7/2	52/9/3	0.96
Indication for transplant (ILD/COPD/CF/Other)	22/16/5/5	29/23/7/5	0.99
Single lung transplant, *n* (%)	8 (16.7)	10 (15.6)	0.88
Best post-transplant FEV_1, L	2.45 ± 0.82	2.38 ± 0.79	0.65
Time to CLAD onset post-transplant, months	38 (24–62)	43 (27–69)	0.28
CLAD phenotype (BOS/RAS/other)	33/11/4	45/15/4	0.92
CLAD stage at index date (1/2/3/4)	4/28/13/3	6/38/16/4	0.94
Baseline ANC, cells/μL	4,350 ± 1,900	4,620 ± 2,200	0.51
Baseline ALC, cells/μL	1,150 ± 480	1,080 ± 520	0.47
Baseline DSA status, *n* (%)	14 (29.2)	22 (34.4)	0.56
Pre-index FEV_1 slope, mL/day	-1.88 ± 0.65	-1.78 ± 0.59	0.39
Azithromycin use, *n* (%)	37 (77.1)	52 (81.2)	0.60
Extracorporeal photopheresis use, *n* (%)	6 (12.5)	9 (14.1)	0.81

Values are reported as mean ± SD, median (IQR), or *n* (%). ANC, absolute neutrophil count; ALC, absolute lymphocyte count; DSA, donor-specific antibody.

Among ATG-treated patients, the median time from CLAD diagnosis to ATG was *58* days (IQR 34–89). Rabbit ATG was used in *85.9%* (n=55), while equine ATG was used in *14.1%* (n=9). Baseline maintenance immunosuppression and prophylactic antimicrobial strategies were broadly similar across groups.

3.2 Clinical Effectiveness

Among the *58* ATG-treated patients included in the primary spirometric analysis, the mean rate of FEV_1 decline before treatment was *-1.78 mL/day* (95% CI -1.96 to -1.60). During the 6 months after ATG, the mean rate of decline changed to *-1.49 mL/day* (95% CI -1.65 to -1.33), corresponding to an absolute slope difference of *0.29 mL/day* (95% CI 0.01–0.57, p=0.04) and a relative attenuation of *16.3%*. Individual and mean FEV_1 trajectories are shown in Figure 2.

A complete response, defined as a positive post-treatment FEV_1 slope, was observed in *8.6%* (n=5) of patients. A partial response, defined as greater than 20% attenuation of the pre-treatment rate of decline, was observed in *69.0%* (n=40). The remaining *22.4%* (n=13) were classified as nonresponders. Absolute FEV_1 at 3 months changed by a median of *+5 mL* (IQR -35 to +45), and at 6 months by a median of *-20 mL* (IQR -65 to +20) relative to the index date.

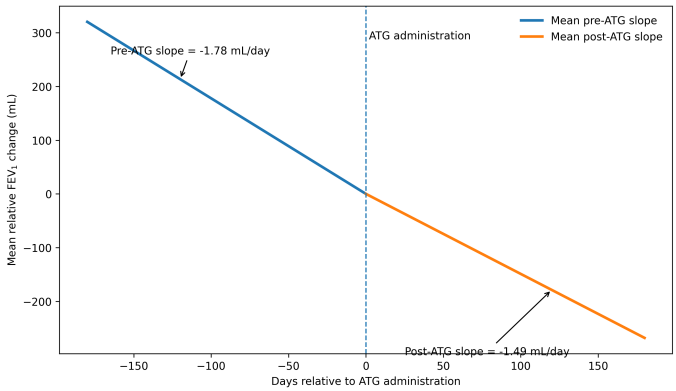

Figure 2. Individual and mean FEV_1 trajectories in the 6 months before and after ATG administration among treated patients with rapidly progressive CLAD.

Patients with at least a partial response had a baseline pre-ATG rate of decline of *-2.05 mL/day* (IQR -2.40 to -1.70), compared with *-1.25 mL/day* (IQR -1.55 to -0.95) among nonresponders (p=0.01). In univariable analysis, faster pre-treatment decline was associated with response (OR 1.38 per 0.5 mL/day steeper decline, 95% CI 1.02–1.88, p=0.04). These data are presented in Table 2.

Table 2. Comparison of baseline characteristics by response to ATG among treated patients with adequate spirometric follow-up (n=58).

Variable	Nonresponse (n=13)	Partial response (n=40)	Complete response (n=5)	*p* value
Age at transplantation, years	55.8 ± 11.2	54.2 ± 12.5	56.1 ± 13.1	0.85
Male sex, *n* (%)	8 (61.5)	24 (60.0)	3 (60.0)	0.99
Best post-transplant FEV_1, L	2.40 ± 0.75	2.37 ± 0.81	2.42 ± 0.78	0.97
Time to CLAD onset, months	40 (26–68)	42 (28–71)	44 (30–65)	0.88
Time to ATG after CLAD onset, days	70 (42–110)	55 (36–85)	50 (32–78)	0.29
CLAD phenotype (BOS/RAS/other)	8/4/1	31/7/2	4/1/0	0.86
CLAD stage at time of ATG (1/2/3)	1/7/5	5/26/9	0/4/1	0.72
Baseline ANC, cells/μL	4,250 ± 1,800	4,750 ± 2,300	4,100 ± 1,600	0.64
Baseline ALC, cells/μL	1,180 ± 450	1,050 ± 530	1,120 ± 490	0.70
Baseline DSA status, *n* (%)	5 (38.5)	14 (35.0)	2 (40.0)	0.95
Pre-ATG FEV_1 slope, mL/day	-1.25 ± 0.35	-2.05 ± 0.68	-2.20 ± 0.75	<0.001
Rapid decliner (>100 mL/mo), *n* (%)	7 (53.8)	36 (90.0)	5 (100)	0.01
Type of ATG (rabbit/equine)	11/2	35/5	4/1	0.94

Partial response was defined as > 20% attenuation in the rate of FEV_1 decline; complete response was defined as a positive post-treatment FEV_1 slope.

When the untreated comparator group was examined over a matched post-index interval, the change in FEV_1 slope was *-0.15 mL/day* in controls versus *0.29 mL/day* in ATG-treated patients. The between-group difference was *0.44 mL/day* and remained significant after adjustment (p = 0.046).

3.3 Survival

Over a median follow-up of *31.2* months (IQR 19–45), *41* graft-failure events occurred in the full ATG cohort

(n=64) and *34* in the untreated cohort (n=48). In the propensity-matched analysis (40 pairs), median graft survival from onset of rapidly progressive CLAD was *28.4 months* (95% CI 22.3–36.8) in ATG-treated patients and *19.2 months* (95% CI 14.5–25.6) in untreated patients (Figure 3). The hazard ratio for graft failure associated with ATG treatment was *0.71* (95% CI 0.46–1.09, p=0.12).

Interpretation: This result did not reach statistical significance (p=0.12). The 95% confidence interval includes the null value (HR=1.0) and ranges from potential benefit (HR=0.46) to potential harm (HR=1.09). Therefore, these survival findings are exploratory and inconclusive. They do not provide sufficient evidence to conclude that ATG confers a survival advantage in this population.

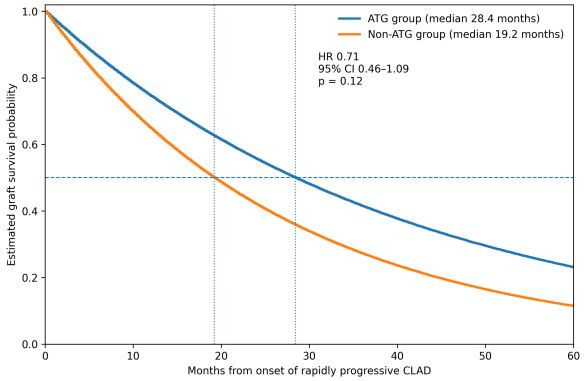

Figure 3. Kaplan–Meier curves for graft survival from onset of rapidly progressive CLAD in propensity-matched ATG and non-ATG cohorts. The difference in survival did not reach statistical significance.

Table 3. Univariable and multivariable Cox regression analyses of graft survival after onset of rapidly progressive CLAD.

Variable	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at transplantation (per 10 years)	1.08	0.82–1.42	0.58	–	–	–
Male sex	0.98	0.63–1.52	0.92	–	–	–
Single lung transplant	1.28	0.72–2.28	0.40	–	–	–
Best post-transplant FEV_1 (per 1L)	0.82	0.59–1.14	0.24	–	–	–
Time to CLAD onset (per 12 months)	0.96	0.88–1.05	0.38	–	–	–
BOS phenotype	0.89	0.54–1.47	0.65	–	–	–
RAS phenotype	1.35	0.82–2.22	0.24	–	–	–
Stage 3–4 CLAD at index	1.48	0.94–2.33	0.09	1.38	0.86–2.21	0.18
Baseline ANC (per 1000 cells/μL)	1.12	1.01–1.24	0.03	1.10	0.99–1.22	0.07
Baseline ALC (per 500 cells/μL)	0.91	0.76–1.09	0.30	–	–	–
Pre-index FEV_1 slope (per 0.5 mL/day)	1.06	0.93–1.21	0.38	–	–	–
Receipt of ATG	0.71	0.46–1.09	0.12	–	–	–

Within the ATG cohort, univariable Cox regression identified higher baseline absolute neutrophil count as a predictor of poorer graft survival, with a hazard ratio of *1.12 per 1000 cells/μL increase* (95% CI 1.01–1.24, p=0.03). However, in multivariable analysis adjusting for CLAD stage and phenotype, baseline ANC was no longer statistically significant (HR 1.10 per 1000 cells/μL, 95% CI 0.99–1.22, p=0.07). This suggests that the association between ANC and graft survival may be confounded by other clinical factors. Results of survival modeling are provided in Table 3.

3.4 Safety

Within 6 months after ATG administration, infectious complications occurred in *27.6%* (n=16) of treated patients. Bacterial pneumonia was the most common event, occurring in *15.5%* (n=9) of patients, followed by viral respiratory infection (*6.9%*, n=4), urinary tract infection (*3.4%*, n=2), and *Clostridioides difficile* infection (*3.4%*, n=2). Opportunistic infections (including aspergillosis and CMV pneumonitis) occurred in *3.4%* (n=2). Infection-related hospitalization was required in *19.0%* (n=11), and *2* patients (3.4%) required intensive care admission.

Table 4. Safety outcomes within 6 months after ATG administration.

Outcome	n (n=58)	%
Any infectious complication	16	27.6
Bacterial pneumonia	9	15.5
Viral respiratory infection	4	6.9
Fungal pneumonia	1	1.7
Mycobacterial infection	0	0.0
Urinary tract infection	2	3.4
Suspected skin/soft tissue infection	1	1.7
Gastrointestinal infection	2	3.4
Hospitalization for infection	11	19.0
ICU admission	2	3.4
New neutropenia (ANC <1000)	12	20.7
New lymphopenia (ALC <500)	14	24.1
New thrombocytopenia (platelets <100,000)	10	17.2
Infusion-related reaction	8	13.8
Premature discontinuation of therapy	2	3.4
New malignancy during follow-up	3	5.2

New or worsened cytopenia developed in *36.2%* (n=21) after treatment, with neutropenia (ANC <1000 cells/μL) in *20.7%* (n=12), lymphopenia (ALC <500 cells/μL) in *24.1%* (n=14), and thrombocytopenia (platelets <100,000/μL) in *17.2%* (n=10). Infusion-related adverse reactions (fever, chills, rash, or hypotension) occurred in *13.8%* (n=8) and led to premature discontinuation of therapy in *2* patients (3.4%). During longer follow-up (median 24 months post-ATG), new malignancy was identified in *5.2%* (n=3), including nonmelanoma skin cancer (n=2) and post-transplant lymphoproliferative disorder (n=1). Safety outcomes are detailed in

Table 4.

4 Discussion

This retrospective cohort study evaluated ATG in a clinically distinct subgroup of lung transplant recipients with rapidly progressive CLAD, a population in whom therapeutic urgency is high and the margin for clinical deterioration is narrow. The principal finding was that ATG was associated with a modest attenuation in the rate of FEV_1 decline over the 6 months following treatment. Although absolute recovery in lung function was uncommon, a substantial fraction of patients (69.0%) achieved at least partial stabilization by slope-based criteria, which is broadly consistent with prior single-center ATG series [14–16, 18]. In the setting of rapidly progressive CLAD, even deceleration of decline may be clinically meaningful because untreated disease often proceeds quickly toward respiratory disability, retransplantation, or death [2, 3].

The functional benefit observed in this study should be interpreted within the biological and clinical context of progressive CLAD. Rapid decline in FEV_1 may identify a subgroup with a still-active inflammatory or alloimmune component that remains partly modifiable by intensified immunosuppression. At the same time, the heterogeneity of CLAD means that not all rapidly progressive cases are equally likely to respond. Patients with advanced fibrotic remodeling, restrictive physiology, recurrent infection, or mixed injury patterns may derive less benefit from cytolytic therapy than patients with earlier-stage obstructive decline [4, 5, 7]. The present analysis suggests that faster pretreatment decline may help identify patients more likely to respond (OR 1.38 per 0.5 mL/day steeper decline, 95% CI 1.02–1.88, p=0.04), although these associations require validation in larger cohorts [16].

4.1 Survival Findings: Exploratory and Inconclusive

The survival findings require particularly careful interpretation. In this study, the observed hazard ratio for graft failure associated with ATG treatment was 0.71 (95% CI 0.46–1.09, p=0.12). *By conventional statistical standards ($p<0.05$), this result is not statistically significant.* Several interpretations are possible: (1) there is no true survival benefit, and the observed difference is due to chance; (2) there is a modest survival benefit that this study was underpowered to detect; or (3) unmeasured confounding in this non-randomized design accounts for the observed difference. The wide confidence interval includes the null value (HR=1.0) as well as potential benefit (HR as low as 0.46) and potential harm (HR as high as 1.09).

Therefore, these survival results should be considered exploratory and inconclusive. They do not provide sufficient evidence to claim a survival advantage for ATG in rapidly progressive CLAD. This interpretation is consistent with the caution expressed in prior ATG cohorts [16, 18], none of which have demonstrated a statistically significant survival benefit in this setting.

4.2 Safety: A Clinically Important Concern

Safety remains central to any evaluation of ATG in CLAD. In this cohort, infectious complications occurred in 27.6% of treated patients within 6 months, with bacterial pneumonia as the most common event (15.5%). This infection burden is clinically significant and reflects the combined effects of lymphocyte depletion, baseline transplant-related immunosuppression, structural lung vulnerability, and repeated healthcare exposure [15, 18, 19]. Hematologic toxicity (cytopenias in 36.2%) and treatment intolerance (infusion reactions in 13.8%) were also observed. These findings reinforce that ATG should not be considered a benign escalation strategy and that treatment decisions must weigh the potential for functional stabilization against the substantial risk of infectious and hematologic harm.

4.3 Methodological Limitations and Inference

Several important methodological limitations affect the interpretability of these findings.

Small comparator group. The untreated comparator group included only 48 patients with rapidly progressive CLAD. This small sample size limited the maximum number of propensity-matched pairs to 40, which provided limited statistical power to detect modest survival differences. The wide confidence interval around the hazard ratio (0.46 to 1.09) reflects this imprecision. A larger comparator group would have allowed more stable matching and more precise effect estimation.

Confounding by indication. In this retrospective salvage therapy study, the decision to administer ATG was non-random and clinician-dependent. Clinicians typically reserve ATG for patients perceived to be deteriorating most rapidly or those who have failed

other therapies. While we attempted to balance measured confounders using propensity scores (including pre-index FEV_1 slope, CLAD stage, and phenotype), we cannot rule out confounding by unmeasured variables such as physician judgment, patient frailty, infection burden, or social support. Propensity matching cannot substitute for randomization. Therefore, the observed association between ATG and survival should not be interpreted causally.

Inability to perform phenotype-specific analysis. Rapidly progressive CLAD includes both BOS and RAS phenotypes, which may have different pathobiology and potentially different responses to ATG. However, the sample size (only 45 BOS and 15 RAS patients in the ATG group) precluded meaningful phenotype-specific subgroup analysis. It is possible that ATG is more effective in one phenotype than the other, but this study cannot answer that question.

Non-standardized spirometric surveillance. Although all patients underwent routine spirometry according to institutional protocols, the timing and frequency of measurements varied based on clinical stability and patient adherence. The use of linear regression to estimate FEV_1 slopes assumes a linear trajectory, which may not fully capture nonlinear progression, intermittent exacerbations, or informative dropout due to death or retransplantation.

Generalizability. This was a single-center study from a large academic transplant center. ATG protocols, dosing regimens, prophylactic antimicrobial strategies, and thresholds for salvage therapy vary substantially across transplant programs. Therefore, these findings may not generalize to centers with different practice patterns.

Why these methods are adequate for hypothesis generation. Despite these limitations, the analytical approach is appropriate for the research question and data available. Propensity matching is the standard method for reducing confounding in non-randomized treatment comparisons when randomization is infeasible. The use of trajectory-based spirometric analysis (pre/post slopes) is a validated method for assessing treatment response in CLAD. The Cox proportional hazards model is the standard approach for time-to-event analysis in transplant outcomes research. However, given the limitations described above, these results should be interpreted as hypothesis-generating rather than practice-changing. They provide a signal that merits investigation in adequately powered prospective randomized trials, but they do not constitute definitive evidence of effectiveness.

What this study can and cannot conclude. This study can conclude that ATG was associated with a modest, statistically significant attenuation in the rate of FEV_1 decline over 6 months ($p=0.04$). This study cannot conclude that ATG improves survival, because the survival difference was not statistically significant ($p=0.12$) and the confidence interval included the null. This study can conclude that ATG is associated with a substantial burden of infectious complications (27.6%) and hematologic toxicity (36.2%). This study cannot conclude that ATG should be used routinely in rapidly progressive CLAD; at most, it suggests that carefully selected patients may experience functional stabilization, but this must be weighed against significant toxicity.

4.4 Clinical and Research Implications

Despite these limitations, the present study addresses a clinically consequential question: whether ATG has a role in patients whose lung function is declining fast enough that simple observation is unsatisfactory. The findings suggest that ATG may provide measurable functional stabilization in a subset of such patients, but that this potential benefit is accompanied by appreciable toxicity. *However, because no statistically significant survival benefit was detected, these findings are hypothesis-generating rather than practice-changing.*

The totality of evidence from this study does not support the routine use of ATG in rapidly progressive CLAD. Instead, these findings suggest that ATG may have a role only in carefully selected patients after thorough discussion of the uncertain benefits and well-documented risks. The non-significant survival finding should not be interpreted as evidence of effectiveness, but rather as a signal that merits investigation in adequately powered prospective studies.

Prospective multicenter randomized trials are urgently needed to define optimal candidate selection, timing of therapy, dosing strategy, comparative effectiveness against other salvage approaches (azithromycin, extracorporeal photopheresis, total lymphoid irradiation), and most importantly, to determine whether any survival benefit exists at all [11–13, 20–23].

5 Conclusion

Among lung transplant recipients with rapidly progressive CLAD, ATG was associated with modest, statistically significant attenuation of FEV_1 decline over 6 months (mean difference 0.29 mL/day, 95% CI 0.01–0.57, p=0.04). However, no statistically significant survival benefit was detected (HR 0.71, 95% CI 0.46–1.09, p=0.12). Treatment was accompanied by a substantial burden of infectious complications (27.6%) and hematologic toxicity (36.2%).

These findings are hypothesis-generating, not practice-changing. Due to the small comparator group (n=48), the potential for confounding by indication, the lack of statistical power, and the wide confidence intervals around the survival estimate, these results should not be interpreted as definitive evidence of effectiveness.

The study does not support routine use of ATG in rapidly progressive CLAD. Any use should be limited to carefully selected patients after thorough risk-benefit discussion that acknowledges the uncertainty regarding survival benefit and the substantial risk of toxicity. Prospective randomized trials are urgently needed to determine whether any survival benefit exists and to establish the optimal risk-benefit profile for this therapy.

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