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Outcomes Following ATG Therapy for Chronic Lung Allograft Dysfunction

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Background. Chronic lung allograft dysfunction (CLAD) is the major factor limiting survival post lung transplantation (LTx) with limited effective therapeutic options. We report our 12-y experience of antithymocyte globulin (ATG) as second-line CLAD therapy. **Methods.** Clinical and lung function data were collected on LTx patients receiving ATG. Rate of FEV1 decline (mL/d) was calculated before and after ATG. Partial response to ATG was defined by rate of FEV1 decline improving 20%. Complete response was defined by an absolute improvement or stability in baseline FEV1. **Results.** Seventy-six patients received ATG for CLAD. Of these, 5 patients who had a clinical diagnosis of antibody-mediated rejection and were treated with plasmapheresis before or after ATG were excluded from analysis. Sixteen (23%) were complete responders, 29 (40%) were partial responders, and 26 (37%) did not respond. Those with CLAD stage 2 or 3 and younger age were more likely to respond. Partial responders had a 65% lower risk of death or retransplant (HR, 0.35; $P=0.003$), whereas complete responders reduced their risk by 70% (HR, 0.30; $P=0.006$). **Conclusions.** ATG appears to stabilize or attenuate lung function decline in CLAD, which may lead to improved retransplant-free survival. Although certain predictors of response have been identified in this large single-center review, these findings need to be confirmed by a multicenter randomized-controlled trial to determine predictors of response to ATG for CLAD.

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INTRODUCTION

Although outcomes following lung transplantation (LTx) have improved significantly over the past 3 decades, they remain significantly worse than other solid organ transplant outcomes, with a median post-LTx survival of only 6 y.[1] The leading cause of morbidity and mortality post LTx is allograft failure, the definition of which has evolved over time.[2]

Chronic lung allograft dysfunction (CLAD) is a heterogeneous diagnosis with different phenotypes, predominantly obstructive and restrictive, and variable prognoses.[2] Despite changes in the diagnostic criteria and greater understanding of pathophysiology, effective therapeutic options remain limited. Furthermore, there is no international consensus on the treatment of CLAD with considerable differences among transplant centers. First-line approaches may include the addition of azithromycin, alteration of baseline immunosuppression, and augmentation of immunosuppression with high-dose intravenous methylprednisolone.[3] LTx recipients with de novo donor-specific antibodies (DSAs) and a clinical diagnosis of antibody-mediated rejection (AMR) are traditionally managed with plasmapheresis and B cell–modulating therapies.[4] In the absence of anti-HLA DSA, there is no universally agreed approach to management if initial therapies fail to stabilize lung function.

Antithymocyte globulin (ATG) is a concentrated polyclonal anti-human T-lymphocyte immunoglobulin preparation derived from horses and rabbits after injection with a T-lymphocyte cell line. Therapy with ATG depletes circulating lymphocytes, including alloreactive cytotoxic T cells, leading to a reduction in the production of inflammatory cytokines, which may contribute to CLAD development.[5] Historically, ATG has been utilized as induction immunosuppression in renal transplantation[6] with limited utilization in other solid organ transplantation.[7,8]

Although there are some data suggesting ATG may confer benefit as induction therapy and for acute cellular rejection

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(ACR) in LTx,[9,10] there is a paucity of data surrounding its role as a treatment option for established CLAD. Five studies have been published to date with variable results, including 3 published in the early era of lung transplantation before tacrolimus-based immunosuppression regimes.[11-15] The 2 more recent studies by Izhakian et al[14] and January et al[15] have demonstrated conflicting results. Based on the paucity of contemporary data, we examined our center's experience of using ATG as second-line therapy for CLAD.

MATERIALS AND METHODS

Data Collection

We examined a retrospective cohort of LTx recipients from January 2006 to December 2017 receiving ATG as second-line therapy for CLAD after intravenous methylprednisolone. Data were censored at death or retransplant or cessation of follow-up (December 2018) with a median follow-up period of 63 months (range, 9–300).

Patient demographics, underlying diagnosis for LTx, cytomegalovirus (CMV) serostatus, and post-LTx episodes of replication, lung function (forced expiratory volume over 1 second [FEV1], forced vital capacity [FVC], FEV1/FVC ratio, and total lung capacity [TLC]), baseline immunosuppression regimen, CLAD phenotype and stage, total white cell count, lymphocyte and neutrophil count, CD2 and CD3 lymphocyte count, immunoglobulin G (IgG) levels, microbiology pre and post ATG, presence of DSAs, and any additional immunosuppression were collected from the Alfred Hospital electronic and paper-based medical records. Presence and stage of primary graft dysfunction at 72 h post LTx and ACR in transbronchial biopsy samples were also reviewed. CLAD stage was defined by spirometry and radiology parameters at the time of ATG commencement as a proportion of baseline lung function as defined by recent international consensus guidelines and the presence or absence of persistent chest opacities on computed tomography[2] and stratified into obstructive (BOS) and restrictive (restrictive allograft syndrome [RAS]) phenotypes. The study was approved by the Alfred Ethics and Research Committee (project number 581/18).

Lung function changes were measured by rate of decline in FEV1 (mL/d) in the 6 mo before and after ATG administration. Those who received additional therapy within the 6-mo period had lung function measures truncated to when additional therapy was commenced. A clinical response to ATG was defined by an absolute improvement or stability of FEV1 (complete response) or the by rate of FEV1 decline improving by 20% or more (partial response).

Management Protocol

LTx recipients receive standard triple immunosuppression, infection prophylaxis, routine surveillance investigations, and follow-up. Further details are provided in Supplement 1 (SDC, http://links.lww.com/TXD/A316).

All patients were commenced on azithromycin when CLAD was suspected, and this was generally well tolerated. First-line augmentation of immunosuppression for all patients with CLAD was a 3-d course of intravenous methylprednisolone at 10 mg/kg/d as is routine management at our center. Patients with positive DSA results and a clinical suspicion of AMR were then treated with plasmapheresis ± IVIg. Those without DSAs who continued to have declining lung function despite methylprednisolone were treated with ATG if deemed appropriate by the treating physician. The main exclusion criteria for ATG were significant infection burden given the concern of uncontrollable sepsis due to profound T-cell immunosuppression associated with ATG. The other main exclusion criteria were FEV1 below 20% predicted with ongoing decline given these patients were in the preterminal phase of their disease and therefore unlikely to benefit from therapy.

ATG administration was performed over a 5-d course. Patients received premedications (intravenous methylprednisolone 100 mg for first dose and 25 mg for subsequent doses, intravenous promethazine 25 mg, and oral paracetamol 1000 mg). The initial dose administered was 500 mg for equine ATG (ATGAM, Pfizer) and 300 mg for rabbit ATG (Grafalon, previously ATG-Fresenius S) with subsequent dosing based on T-cell responses as measured by daily CD2 and CD3 lymphocyte counts with a target range of 20–150 per mcL. All ATG was prepared by on-site pharmacy in 500 mL of 0.9% sodium chloride and administered over a 4- to 6-h period.

Equine ATG was prescribed for initial therapy for most patients, except when unavailable, in which case rabbit ATG was administered first line.

Patients whose lung function continued to decline were subsequently treated with a second course of ATG, usually rabbit, if deemed clinically appropriate by the treating physician, which was largely determined by infection episodes, absolute lung function as well as suitability of other treatment options such as extracorporeal photopheresis (ECP) and retransplantation.

CMV prophylaxis was recommenced for 3 mo for all patients undergoing ATG with careful surveillance for infections with bronchoscopy pre and post ATG administration. Baseline immunosuppression was also adjusted on an individual basis by the treating physician.

Statistical Analysis

Continuous variables were summarized using mean (SD) or median (interquartile range) according to data type and distribution. Categorical variables were expressed as counts and proportions. The Kaplan-Meier method was used to plot transplant-free survival as a function of time, and comparisons between curves were made with the log-rank test. Univariate and multivariate analyses for retransplant-free survival were performed using Cox proportional hazards regression, with results reported as hazard ratios and 95% confidence intervals (95% CI). Variables with a $P < 0.05$ on univariate analyses or those deemed to be clinically relevant were entered in a hierarchical regression model to identify the factors independently associated with retransplant-free survival. Comparisons between responders and nonresponders were made using Student *t*-test, Wilcoxon rank-sum test, chi-square, or Fisher's exact where appropriate. All calculated *P* values were 2-tailed with a $P < 0.05$ indicating statistical significance. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics

Seventy-six patients received ATG for CLAD over the 12-y period examined.

Eighty-seven percent of patients had an obstructive CLAD phenotype. Twenty-five (33%) patients had DSAs before commencing ATG; however, only 5 (7%) had a clinical diagnosis of AMR with a mean fluorescence index (MFI) of >5000 and were treated with plasmapheresis before or after ATG. These 5 patients were excluded from the analysis. The demographics of the remaining 71 patients are outlined in Table 1.

All patients with CLAD were commenced on azithromycin, and this was well tolerated with only 5 (6.6%) patients discontinuing it due to intolerance.

Response

As per our definition of response, 63% were clinical responders, including 23% complete responders and 40% partial responders. The mean rate of FEV1 decline in the responder cohort improved from 6.5 to 1.6 mL/d ($P = 0.0001$). Responders had improved retransplant-free survival, with a 65% reduction in risk in death or retransplant (HR, 0.35; 95% CI, 0.18-0.70; $P = 0.003$) in partial responders and a 70% reduction in complete responders (HR, 0.30; 95% CI, 0.13-0.71; $P = 0.006$). Clinical responders had improved retransplant-free survival (Figure 1A and B).

On multivariate analysis, those who had ACR during their clinical course and less severe CLAD (stage 1 or 2) were also more likely to have improved retransplant-free survival (Table 2).

In the nonresponder cohort, the mean FEV1 rate of decline increased from 4.4 to 7.0 mL/d ($P = 0.008$). There was no difference in the type of ATG product used between the 2 cohorts.

Predictive Clinical Variables

Age, indication for LTx, and CLAD stage were predictors of partial response. Those who were younger at time of LTx were more likely to respond (46.3 versus 54.5 y; $P = 0.038$). Those who were transplanted for COPD were less likely to respond (73.1% versus 42.2%; $P = 0.012$) compared with other indications for LTx. When stratified for CLAD stage, those with CLAD stage 2 or 3 were more likely to have a partial response compared with stage 1 (OR, 2.37; 95% CI, 1.33-4.21; $P = 0.003$). CLAD phenotype, however, did not correlate with response.

Clinical variables were not identified to predict those patients with a complete response to ATG.

Achieving target CD2/CD3 T-lymphocyte reduction was universal in the rabbit ATG group but only demonstrated in 61% of the equine ATG group; however, this did not predict clinical response.

Recurrent ATG Therapy

Twenty-one patients received ATG twice with a median interval of 3 mo (range, 1–25), equine followed by rabbit in all but 1 case. Four patients had a treatment interval of >6 mo, having been partial responders after the first course of ATG and subsequently partially responded to the second course also. Eight patients were partial responders to the second ATG course having not responded to the first course. Two patients had a partial response to equine ATG with a subsequent complete response to rabbit ATG. Two patients did not respond with either ATG course. Having received rabbit ATG for the second course, 20 patients achieved target CD2/3 levels, but this did not correlate with response. Sixteen (76%) patients died or underwent retransplant during the follow-up period.

Complications

ATG therapy was well tolerated by the cohort overall without need for premature cessation. One-third of patients cultured new microbial organisms post ATG administration at

TABLE 1.

Patient demographics

	Responders (n = 45)	Nonresponders (n = 26)	*P*
Age at LTx (mean, SD)	46.3 (17.1)	54.5 (12.7)	0.038
Male, n (%)	28 (62.2)	11 (42.3)	0.10
Type of LTx (%)			
BSLTx	92	86	0.55
Single LTx	4	7	
Redo BSLTx	2	7	
HLTx	2	-	
Indication for LTx (%)			
COPD	41	70	0.014
ILD	20	11	0.36
CF	24	7	0.12
PAH	4	0	0.54
Other	6	4	1.00
ACR, n (%)	18 (40)	9 (34.6)	0.65
PGD, n (%)	20 (44.4)	8 (30.8)	0.26
DSAs, n (%)	11 (24.4)	9 (34.6)	0.36
CMV reactivation, n (%)	11 (24.4)	11 (42.3)	0.12
Baseline immunosuppression regimen (%)			
Tacrolimus-based	40 (88.9)	20 (76.9)	0.19
Cyclosporin-based	2 (4)	2 (7)	
Everolimus-based	3 (6)	4 (15)	
Mycophenolate (vs Azathioprine)	26 (53)	19 (70)	
Alteration with CLAD diagnosis	7 (14)	6 (22)	
CLAD phenotype (%)			
Obstructive	86	78	0.67
Restrictive	10	15	
Mixed/undefined	4	7	
CLAD stage n (%)			
Stage 1	8 (17.8)	7 (26.9)	0.005
Stage 2	13 (28.9)	15 (57.7)	
Stage 3	9 (20)	4 (15.4)	
Stage 4	15 (33.3)	0 (0)	
Time to CLAD post LTx (d) (median, IQR)	761 (457–1551)	640 (395–1185)	0.22
Time to ATG post-CLAD (d) (median, IQR)	96 (44–160)	57 (41–94)	0.11
ATG product, n (%)			
Equine	35 (77.8)	19 (73.1)	0.65
Rabbit	10 (22.2)	7 (26.9)	
WCC (mean, SD)	7.91 (2.24)	7.66 (3.07)	0.70
Neutrophil count (mean, SD)	5.89 (2.32)	5.69 (2.71)	0.74
Lymphocyte count (mean, SD)	1.24 (0.76)	1.23 (0.77)	0.95
CD2 and CD3 lymphocyte count targets achieved, n (%)	31 (68.9)	17 (65.4)	0.76
New organisms post ATG, n (%)	18 (40)	8 (30.8)	0.44
Serious infection post ATG, n (%)	3 (6.7)	3 (11.5)	0.66

ACR, acute cellular rejection; ATG, antithymocyte globulin; BSLTx, bilateral sequential lung transplantation; CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DSAs, donor-specific antibodies; HLTx, heart-lung transplantation; ILD, interstitial lung disease; IQR, interquartile range; LTx, lung transplantation; PAH, pulmonary arterial hypertension; PGD, primary graft dysfunction; WCC, white cell count.

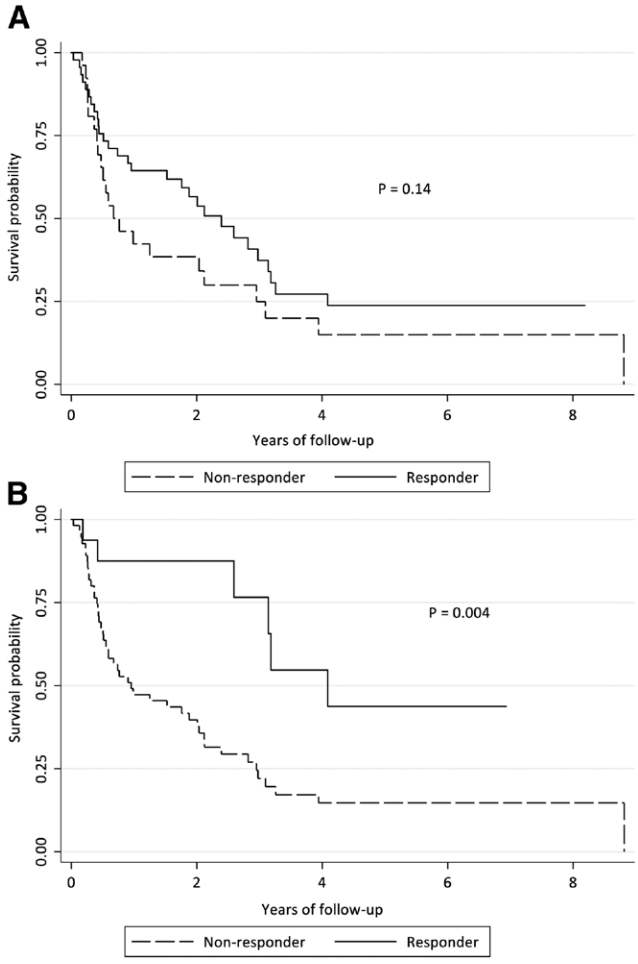

FIGURE 1. A, Kaplan-Meier survival curve showing retransplant-free survival among responders and nonresponders where response is defined by FEV1 decline attenuated by 20% or more post ATG. B, Kaplan-Meier survival curve showing retransplant-free survival among those who improved or stabilized FEV1 post ATG (responder) compared with those who continued to decline (nonresponder). ATG, antithymocyte globulin; FEV1, forced expiratory volume in the first second of expiration.

a median of 5 mo posttherapy (range, 1–54 mo); however, only 4% required hospitalization for infectious complications within the early period (<3 mo) post ATG administration. One patient died of fungal pneumonia and sepsis 3 mo post ATG; however, no other deaths were attributable to infection.

DISCUSSION

This single-center experience examining the use of ATG as a therapeutic strategy for CLAD demonstrates that ATG may improve the rate of FEV1 decline in a significant proportion of patients with CLAD and this may be associated with improved retransplant-free survival. Although complete responders had slightly better retransplant-free survival, those with partial response still had improved outcomes with a 65% reduction in risk of death or retransplant.

The majority of the responder cohort continued to have a decline in FEV1 (partial response); however, this was significantly attenuated, raising the issue of defining treatment response. Although some groups have defined response as complete stabilization or improvement in FEV1,[15] many others, like us, have used attenuated FEV1 decline[14,16] as the benchmark to assess treatment response, given that this is likely to be associated with prolonged survival and delays need for retransplantation, as demonstrated in our cohort. It is unclear whether the attenuated rate of FEV1 decline represents true response or merely the plateau in lung function decline that occurs with limited residual lung function. Nevertheless, even in those with attenuated lung function decline (ie, partial response), there was improved retransplant-free survival.

TABLE 2.

Retransplant-free survival: multivariate analysis

Variable	Hazard ratio	95% CI	*P*
Clinical response	0.35	0.18–0.70	0.003
CLAD stage	1.96	1.40–2.74	<0.0001
ACR	0.50	0.26–0.94	0.033

ACR, acute cellular rejection; CI, confidence intervals; CLAD, chronic lung allograft dysfunction.

Overall, 23% of our cohort improved or stabilized their FEV1 and were complete responders. January et al[15] demonstrated a higher response rate in their rabbit ATG study with 40% improving lung function; however, their treatment cohort included almost 20% with bronchiolitis obliterans syndrome (BOS) stage 0p, which does not fall within the current CLAD criteria that we have utilized. CLAD stage predicted clinical response in our cohort; however, this association does not appear robust. It seems more likely that those with CLAD stages 2–3 had an attenuated rate of FEV1 decline due to lower baseline lung function, as evidenced by the lack of association with CLAD stage with improvement or stabilization in lung function. Furthermore, those with CLAD stage 1 or 2 had better retransplant-free survival, highlighting a discrepancy between response and survival for this variable. This highlights the natural history of CLAD whereby the decline in lung function is attenuated with a lower absolute FEV1, highlighting the differences in prognoses in different stages of CLAD.[2]

With regards to predictors of response, we identified younger age, CLAD stage 2 or 3, and being transplanted for conditions other than COPD as positive predictors on multivariate analysis. This is in contrast to the study by Izhakian et al[14] that suggested that those who stabilized lung function demonstrated lower white cell and lymphocyte count during ATG therapy but found no impact of patient demographics on treatment response. There does not appear to be a biological basis to treatment response being negatively associated with COPD. Although on initial reflection, this may be attributed to older age, the COPD cohort did not differ in age compared with the ILD patients, and therefore it is unclear why those with COPD were less likely to respond.

It is possible that younger patients had more of an immunologically mediated trigger in the development of CLAD, which was able to be attenuated with ATG. Immunosenescence impacts both innate and adaptive immunity. Although there appears to be a pro-inflammatory milieu associated with older age, there is also a reduction in the activation of immune responses seen in younger patients.[17]

ACR on transbronchial biopsy during the initial surveillance period was associated with better retransplant-free survival on multivariate analysis. No patients had active or untreated ACR at the time of undergoing ATG. Those with previously treated ACR did so in the first 12 mo post LTx

when routine surveillance biopsies were undertaken. No patients who had bronchoscopy and transbronchial biopsies for their persistent lung function decline at the time of CLAD diagnosis were found to have ACR. This is important in determining that those who were treated with ATG did have probable or definite CLAD based on current consensus guidelines.[2] It is clear that ACR, while amenable to first-line immunosuppression with pulse methylprednisolone, is associated with adverse later outcomes, including CLAD and poorer long-term survival.[18] This is thought to be largely immunologically triggered and therefore may represent the immunological phenotype of patients that may be responsive to ATG. This highlights the need to look at full clinical course of patients including early transplant outcomes, which may have a significant impact on trajectory long term. Our review of early outcomes included examining many variables, but no other factors such as primary graft dysfunction or CMV reactivations had any impact on survival or lung function response in these cohorts.

Largely related to cost, equine ATG has been first-line and rabbit ATG used if required as a subsequent therapy for CLAD at our institution. In renal transplantation, rabbit ATG has been more effective in depleting lymphocytes in vitro[19] and has been associated with less acute rejection in renal transplantation when used as induction therapy.[20] January et al[14] have utilized rabbit ATG in their cohort, citing a better side effect profile compared with equine ATG. There was no demonstrable difference in tolerability between rabbit and equine ATG in our cohort of patients.

Twenty-one patients in our cohort received ATG twice, equine first, then rabbit in all cases except one. Eight of these patients responded to the second, of course, ATG having failed to respond initially. Given that most patients had equine ATG first and subsequent rabbit ATG with response, it would appear that rabbit ATG had a higher response rate; however, this effect may be due to the attenuation in FEV1 decline occurring with progressive CLAD as the majority of these patients had progressed in CLAD stage at the time of their second ATG therapy.

Although 33% of patients who received ATG have DSAs present, only 7% had significant DSAs (MFI >5000). Those with low-level DSAs present were not deemed to have AMR and therefore were not treated as such but rather treated with ATG when deemed clinically indicated. Fifty percent of these patients had a reduction in MFI with ATG. It is plausible that IVIG neutralized the DSAs[4]; however, there were some who had a reduction in MFI with ATG alone. This is likely due to the immunomodulatory effects of ATG including apoptosis of differentiated CD138+ plasma cells, inhibition of preexisting donor-reactive memory T-cell reconstitution, and preferential reconstitution of T-regulatory cells, all of which affect DSA production.[21] It remains challenging to truly tease out the effect of ATG on DSA production given the small number of patients with DSAs in our cohort, and those with significant DSAs were excluded in the data analysis.

This report has several limitations to highlight. It is single center, and although the sample size is small for robust analysis, this does represent one of the largest studies examining the role of ATG in CLAD. This study is retrospectively analyzed and therefore possibly confounded by era effects. We have attempted to account for this when examining baseline immunosuppression as well as the role of DSAs, which have only been measured routinely in the last 10 years. Furthermore, the retrospective nature of this study means that missing data relating to timing of other interventions as well as lung function at standardized time points pre and post ATG therapy makes further analysis to determine the true effect of ATG challenging. The evolution of the definition of CLAD has also made review of the data problematic. Although we have retrospectively defined our cohort's CLAD status based on the current consensus guidelines,[2] the definition of CLAD at the time of ATG commencement is not necessarily consistent with this. Nevertheless, all those treated with ATG have had a persistent decline in FEV1 by 20% or more from their best result and been stratified into BOS or non-BOS, which makes the applicability of current CLAD definitions reasonable and the use of CLAD treatments appropriate. The highly variable nature and progression of CLAD make any association between ATG therapy and lung function difficult when examining these data, retrospectively, as additional confounding factors may have impacted lung function trajectory. Furthermore, in the absence of case-controls, which would be a historic cohort of CLAD patients who did not receive additional therapy after intravenous methylprednisolone, it remains difficult to draw any conclusions about the trajectory of lung function or how much of an impact on retransplant-free survival ATG truly has. This remains a challenge for all retrospective studies looking at the treatment and outcomes for CLAD. Ideally, prospective randomized trials comparing treatment options for CLAD would provide clarity on the true effect on lung function. In the absence of this, validation of our findings in other LTx cohorts would be useful.

CONCLUSION

This single-center experience suggests that ATG may improve FEV1 or attenuate its rate of decline in patients with CLAD, which can be associated with improved retransplant-free survival. Future clinical trials are needed to confirm this clinical response, determine the ideal phenotype that would benefit from ATG, and define the role of ATG in the treatment algorithm of CLAD.

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