HLA Donor Specific Antibody and HLA Antigen Bias are Independent Risk Factors for Chronic Lung Allograft Dysfunction

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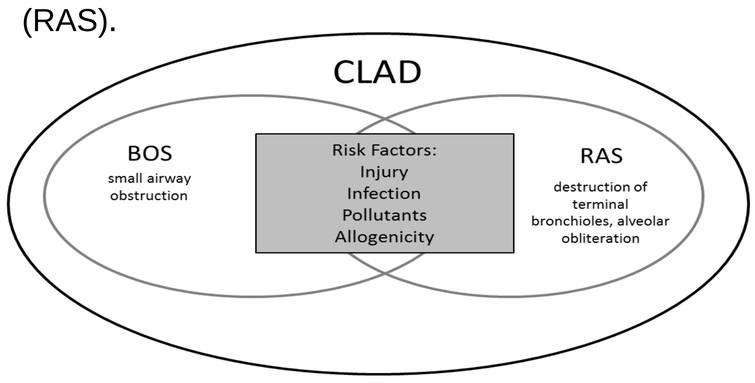
Background

Despite recent advances in medical management of lung transplant patients, the median 5-year survival of recipients remains the lowest among major solid organ allografts. Chronic lung allograft dysfunction (CLAD) is a limiting factor for long-term survival in lung transplant recipients. Bronchiolitis obliterans syndrome (BOS) is the predominant phenotype of CLAD, with the other main phenotype being restrictive allograft syndrome (RAS).



Adapted from Thompson BR, Westall GP, Paraskeva M, and Snell GI. (2014) Respirology 19(8):1097-105.

Although numerous risk factors have been identified so far, the pathological mechanisms of CLAD remain poorly understood. The presence of HLA donor specific antibodies (DSA) correlates with the development of BOS[1]. Furthermore, DSA targeting therapies lower the incidence of chronic dysfunction[2]. Antibodies directed against self antigens, col(V) or K-α1 tubulin, have been associated BOS and clearance of these antibodies reduced the risk of BOS, independent of the clearance of DSA[2]. Furthermore, several studies have suggested that a bias in the HLA-DR antigens may promote a T-cell driven response to self-antigens[3]. Specifically, donor lungs expressing DR15 were found to be more prone to development of BOS post-transplant in a Th17 T-cell dependent manner[3].

Objectives

- To investigate the association of de novo HLA DSA with BOS and RAS
- To compare the HLA genotypes of both recipients and donors to determine if there was any antigen bias associated with either form of CLAD.

Methods

All lung transplant recipients at our facility for whom comprehensive HLA data were available were examined retrospectively, resulting in a total of 92 recipients. Charts were reviewed for each patient and DSA data were recorded, including MFI and date identified. HLA genotype was also examined.

In this study, BOS is characterized by a sustained drop in the FEV1 to less than 80% of the baseline and evidence of obstructive airflow physiology – i.e. the ratio between the FEV1 and the forced vital capacity (FVC) is less than 70%.

RAS is also characterized by a sustained drop in the FEV1 below 80% of the baseline, but in RAS there is no evidence of obstructive physiology – i.e. the FEV1/FVC ratio is preserved at greater than 70%. RAS is often accompanied by signs of actual fibrotic changes on the chest X-ray, but this fibrosis was not considered necessary to make the diagnosis of RAS for this study.

Results

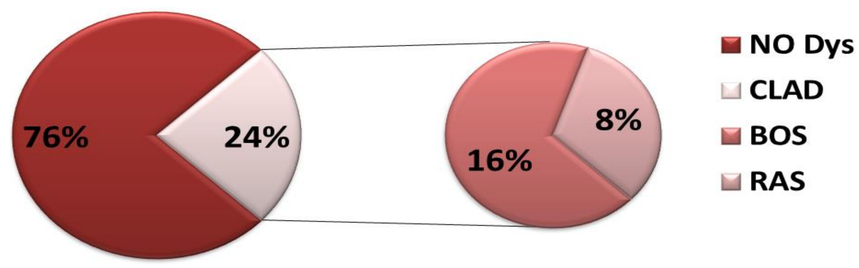


Fig. 1a

Objective 1: *De Novo* HLA DSA: 22 (24%) recipients were identified to have CLAD; 15 (15%) with BOS and 7 (8%) with RAS (Fig. 1a). HLA DSA was identified in 7/15 of the recipients with BOS, compared to only 9/70 recipients in the group with no dysfunction (*p<0.05, Fisher's Exact Test) (Table 1; Fig 1b). Interestingly, none of the RAS recipients had HLA DSA.

Table 1: *Incidence of HLA DSA*

	NEG	POS
BOS	8	7*
CLAD	15	7
NO Dysfunction	60	9

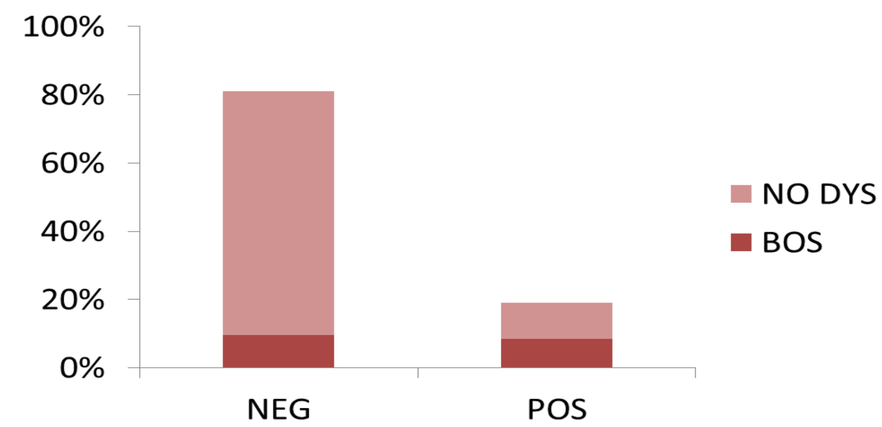


Fig. 1b

Table 2: *Incidence of A3 antigen*

	A3+	A3-
BOS	7	1*
CLAD	7	4
NO Dysfunction	17	37

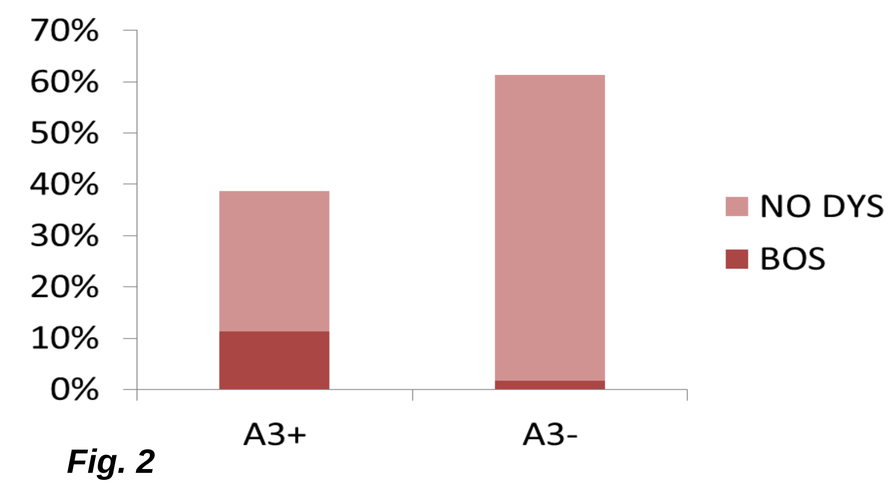


Fig. 2

Objective 2: HLA Genotype Association with CLAD: In our cohort, no bias towards any HLA-DR antigens was observed amongst recipients with CLAD (data not shown). However, the A3 antigen was present in 7/8 recipients with BOS for whom HLA genotype data was available compared to 18/54 recipients in the group with no dysfunction (*p<0.05. Fisher's Exact Test) (Table 2; Fig. 2). No HLA antigen bias was observed in the donors for recipients that developed CLAD compared to the donors for the recipients with no dysfunction.

Conclusions

In summary, de novo HLA DSA and the presence of the A3 antigen were significantly associated with development of BOS. Notably, there was no overlap between the two factors; that is, there did not appear to be any correlation between the presence of the A3 antigen and development of DSA. These findings indicate that development of HLA DSA and antibody directed towards self antigen are two independent mechanisms that lead to CLAD. We did not find any significant correlation between either HLA Class I or Class II DSA with BOS. Nor was there any significant correlation with C1q positivity of DSA in patients with CLAD compared to those without. Additionally, the finding of antigen bias in recipients supports the idea that certain HLA genotypes are associated with development of antibodies to self antigens. Admittedly, the HLA-A3 antigen is very common and our cohort of BOS recipients with available genotype data was small. However, our findings support the idea that certain HLA antigens may be predisposed to display self-antigen peptides after injury, driving development of self-antigen antibodies through Th-17 T-cell dependent mechanisms.

References

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