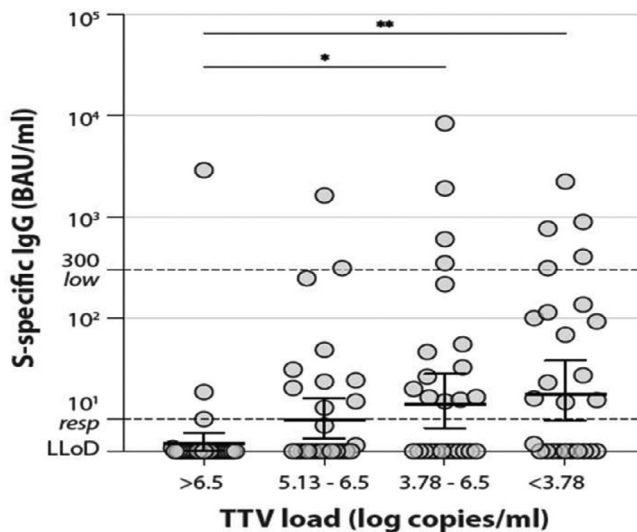




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### Variances in Humoral Responses to Different Spike Protein Domains After SARS-CoV-2 Vaccination in Lung and Heart Transplant Recipients

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**Purpose:** Solid organ transplant recipients are lacking an adequate immune response to SARS-CoV-2 vaccination. Therefore, these patients are still at risk and potentially in need of booster vaccinations. Furthermore, it is important to differentiate between the recipients of distinct organs. The efficacy of SARS-CoV-2 vaccination is usually examined via antibodies specific for the spike protein with assays containing the S1 and receptor-binding-domains (RBD) and rather rarely the S2 domain. To gain information about the humoral response in Tx recipients, it is feasible to compare the immunogenicity of these three domains. To address this, we compared the IgG antibody levels specific for the three spike protein domains in heart (HTx) vs lung (LTx) transplant recipients.

**Methods:** Blood plasma 4-6 weeks after the second dose of SARS-CoV-2 vaccination (85% mRNA) of n=100 LTx and n=40 HTx patients was analysed for S1, S2 and RBD-specific IgG antibodies by Luminex-based multiplex assays. The threshold for positive antibody responses was set separately for each spike domain based on the median MFI + 2σ in an unexposed pre-pandemic control group.

**Results:** For all three spike protein domains, HTx patients showed a significantly higher rate of positive IgG responses than the LTx patients (73% vs 43%). The comparison of MFI values for S1-, S2- and RBD-specific IgG further underlines the superior antibody response by HTx patients with higher MFI values for S1 (p = 0.0001, S2 p = 0.008, RBD p < 0.0001). In the LTx cohort, MFI values for S2- (p < 0.0001) as well as for RBD-specific IgG (p < 0.0001) were higher than for S1. The same applies for S2 vs S1 (p < 0.0001) and RBD vs S1 (p = 0.0018) in the HTx cohort. Comparing the MFI of S2 vs RBD, the levels of domain-specific IgG were higher for S2 than RBD in both LTx (p < 0.0001) and HTx patients (p = 0.0914).

**Conclusion:** HTx patients exhibit a moderately good IgG response to vaccination while LTx recipients show lower antibody responses. Based on the more efficient antibody production against S2 as opposed to the RBD and especially S1-domain, the S2-specific IgG response should be taken into consideration when evaluating the general immune response and the resulting protection after SARS-CoV-2 vaccination in transplant recipients. Both groups of patients might benefit from booster vaccinations.

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### Treatment of De Novo DSA with IVIG Monotherapy After Lung Transplantation

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**Purpose:** The development of de novo donor-specific anti-HLA antibodies (DSA) is associated with worse outcomes in lung transplant recipients (LTxR). The purpose of this study is to evaluate IVIG monotherapy for de novo DSA in the absence of allograft dysfunction or clinical antibody-mediated rejection (AMR).

**Methods:** Adult LTxR between 2/2013 and 3/2021 treated with IVIG monotherapy for de novo DSA with no evidence of AMR were included. IVIG was initiated at 2g/kg followed by 1g/kg monthly for a minimum of 3 months or until clearance (up to 6 months). HLA Ab is routinely checked by Luminex SAB post-transplant at day 14, months 1, 3, 6, 9, 12, and 18, and monthly during IVIG treatment. Primary outcome was change in DSA after IVIG therapy. DSA clearance was defined as sum MFI less than 1000.

**Results:** 32 LTxR developed de novo DSA at a median of 33 days (18,143) post-transplant and were treated with IVIG. Mean follow-up time was 1330 days (861-1910). The median sum MFI for DSA at baseline was 4782 (2927,7490). DQ was the immunodominant DSA in 24 (75%) and only 2 (6%) patients had isolated class I DSA. MFI of sum DSA decreased by a median of 2993 (2051, 6358) after IVIG therapy; p < 0.0001. Eighteen (56%) cleared de novo DSA (Group 1) versus 14 (44%) did not clear (Group 2) at the end of IVIG therapy. There was no significant difference in age, gender, race, transplant indication or type, cPRA, HLA mismatch, or PGD. ACR and AMR tended to be more frequent in Group 2; ACR: 92.9% vs 61.1%, p=0.053; and AMR: 35.7% vs 5.6%, p=0.063. Overall survival for the entire cohort at 1, 3 and 5 years was 100%, 86%, 60%, respectively. There was no significant difference in chronic lung allograft dysfunction (CLAD) or survival between Groups (Table 1).

**Conclusion:** In LTxR, IVIG monotherapy is associated with significant reduction in de novo DSA. DSA clearance may result in less acute rejection. Randomized controlled trials are needed to determine the optimal strategy for managing de novo DSA.

Table 1

Variable	Total Cohort (N=32)	Group 1: DSA Cleared (N=18)	Group 2: DSA Not Cleared (N=14)	p-value
Time from transplant to DSA development, days	33 (18, 143)	32 (29, 38)	105 (16, 361)	0.531
DSA sum MFI, start	4782 (2927, 7490)	3832 (2683, 6548)	5462 (3830, 9770)	0.119
DSA sum MFI, change	-2993 (-6358, -2051)	-3832 (-6548, -2683)	-2576 (-3351, -295)	<0.0001
Immunodominant DSA MFI, start	3611 (2750, 6063)	3239 (2398, 4489)	4038 (2872, 9550)	0.224
Immunodominant DSA MFI, change	-2849 (-4309, -1146)	-3239 (-4489, -2398)	-1231 (-3018, -295)	<0.0001
DSA sum MFI < 1000 at last follow-up	23 (71.9)	16 (88.9)	7 (50)	0.022
IVIG, g/kg/course	5.3 (3.1, 6.2)	3.6 (2.7, 5.5)	6.1 (5.7, 7.2)	0.002
IVIG duration, days	122 (60, 170)	86 (46, 140)	158 (139, 193)	—
IVIG restarted after initial treatment	13 (40.6)	5 (27.8)	8 (57.1)	0.093
ACR	24 (75)	11 (61.1)	13 (92.9)	0.053
ACR grade A2 or greater within 1 year post-transplant	8 (25)	4 (22.2)	4 (28.6)	0.704
AMR	6 (18.7)	1 (5.6)	5 (35.7)	0.063
CLAD	11 (34.4)	8 (44.4)	3 (21.4)	0.266
Patient Survival	22 (68.8)	13 (72.2)	9 (64.3)	0.712

N (%) for categorical data; Median (IQR) for continuous data

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### Carfilzomib versus Rituximab for Treatment of De Novo Donor Specific Antibodies in Lung Transplant Recipients

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**Purpose:** De novo donor-specific antibodies (DSA) increase the risk of chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTxR). Both carfilzomib (CFZ) and rituximab (RTX) lower the mean