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Perivaccination Antimetabolite Hold and Third Dose of SARS-CoV-2 Vaccine in Lung Transplant Recipients: Preliminary Report

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We and others have previously reported suboptimal antibody responses in lung transplant recipients (LTRs) after 2 doses of SARS-CoV-2 mRNA vaccine.[1,2] Immunosuppressive regimens that include antimetabolite therapy (AMT, mycophenolate or azathioprine)[3] and higher doses of AMT[4] have been associated with poorer antibody responses. Safety and efficacy of holding AMT around a third dose of vaccine (D3) is being studied in a randomized trial in kidney and liver transplant recipients (NCT05077254), but the effects in LTRs are unknown. At our center, LTRs who were >1 y posttransplant with no acute cellular or antibody-mediated rejection within 12 mo, were offered the option to hold AMT for 1 wk before and 2 wks after D3 as part of clinical care and not a clinical trial. We performed a retrospective study of LTR who received D3 through October 2021 and who did or did not hold AMT. Demographics, clinical data, donor-specific antibody (HLA-DSA) levels, pulmonary function tests, lung biopsies, and SARS-CoV-2 antibody levels (on EUROIMMUN EIA, positive ≥1.1 arbitrary units, or qualitative DiaSorin assay), obtained as part of clinical care, were extracted from the electronic medical record. This study was approved by the Johns Hopkins Institutional Review Board.

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Of 35 LTRs, AMT was held by 29 (82.9%) and continued by 6 (17.1%) peri-D3. Of these, 23 (65.7%) received mRNA-1273 vaccine, 11 (31.4%) received BNT162b2 vaccine, and 1 received Ad26.COV2.S vaccine for D3. All but 3 received D3 after the FDA's Emergency Use Authorization on August 12, 2021, whereas 3 received D3 of their own volition before that (neither given nor encouraged by our center). Median (interquartile range [IQR]) time between D2 and D3 was 164 (146–188) d (Table 1).

For the AMT-hold group, the median (IQR) anti-S1 post-D3 (6.09 AU [0.58–9.29; n = 24]) was significantly higher than the median (IQR) anti-S1 pre-D3 (0.14 AU [0.08–0.87] [n = 15]) ($P = 0.003$; 1-sided Wilcoxon matched-pairs signed-rank test) (Figure 1). HLA-DSA testing before and after D3 was available for 15 LTRs. HLA-DSA increased after D3 in only 1 of 12 (8.3%) who held AMT versus 0 of 3 who did not hold AMT ($P > 0.9$). Five had lung biopsies post-D3; only 1 (non-AMT–hold group) showed acute rejection.

Pulmonary function tests results within 90 d pre-D3 and 90 ± 45 d post-D3 were available for 24 LTRs (19 who held AMT). Median (IQR) change in FEV1 was −0.01 L (−0.08 to 0.08) for the AMT–hold group and 0.13 L (0.05–0.15) in the non-AMT–hold group.

Limitations include small sample size, especially the non-AMT–hold group, retrospective design, lack of neutralization assays and T-cell and memory B-cell data; however, these preliminary results, including stable DSA and FEV1, lack of acute rejection, and increase in post-D3 SARS-CoV-2 antibody levels in the AMT-hold group, suggest that a brief peri-D3 hold of AMT may be promising for future study. Moreover, increased SARS-CoV-2 antibody levels after D3 may portend a greater increase after D4.[5] We hope this report will support the design of future clinical trials for rigorous evaluation of the AMT-hold strategy to improve antibody responses to SARS-CoV-2 vaccines in LTRs.

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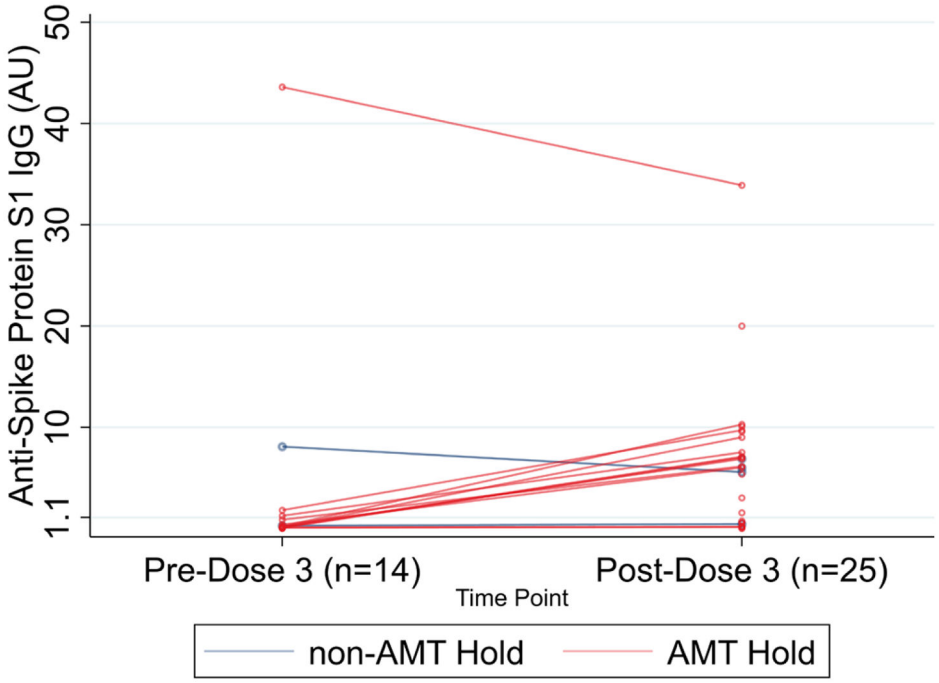

FIGURE 1.

Pre- and post-D3 antibody titers among LTRs stratified by AMT hold. AMT, antimetabolite therapy; LTR, lung transplant recipient.

TABLE 1.

Clinical characteristics of lung transplant recipients who held and did not hold perivaccination antimetabolite therapy

	Overall (n = 35)	Non-AMT hold (n = 6)	AMT hold (n = 29)
Age, median (IQR)	56 (40–65)	66 (45–71)	49 (40–65)
Female sex, no. (%)	20 (57)	4 (67)	16 (55)
Non-White, no. (%)	5 (14)	1 (17)	4 (14)
Hispanic/Latino, no. (%)	1 (3)	1 (17)	0 (0)
Diagnosis, no. (%)			
CF/bronchiectasis	12 (34)	1 (17)	11 (38)
ILD/IPF	10 (29)	2 (33)	8 (28)
COPD/A1ATD	4 (11)	2 (33)	2 (7)
PH/sarcoidosis/HP/BO[d]	6 (17)	1 (17)	5 (17)
Other	3 (9)	0 (0)	3 (10)
Medication included in immunosuppression regimen, no. (%)			
Azathioprine	6 (17)	2 (33)	4 (14)
Cyclosporine	4 (11)	1 (17)	3 (10)
Everolimus	2 (6)	2 (33)	0 (0)
Glucocorticoid[a]	35 (100)	6 (100)	29 (100)
Mycophenolate mofetil	29 (83)	4 (67)	25 (86)
Tacrolimus	30 (86)	5 (83)	26 (90)
Triple Immunosuppression, no. (%)	33 (94)	6 (100)	27 (93)
Mycophenolate total daily dose (mg/d), median (IQR)	1000 (360–1500)	720 (0–1000)	1000 (720–1500)
Glucocorticoid total daily dose >10 mg/d, no. (%)	0 (0)	0 (0)	0 (0)
Years since transplant, median (IQR)	4.4 (2.9–8.8)	3.3 (2.5–8.3)	4.9 (3.2, 8.8)
Days between D2 and D3, median (IQR)	164 (146–188)	148 (99–177)	166 (150–188)
D3 vaccine type, no. (%)			
BNT162b2	11 (31)	2 (33)	9 (31)
mRNA-1273	23 (66)	3 (50)	20 (69)
Ad26.COV2.S	1 (3)	1 (17)	0 (0)
Preexisting positive increase DSA post-D3, no. (%)[b,c]	1 (7)	0 (0)	1 (8)

[a]Glucocorticoid includes prednisone and prednisone equivalents.

[b] The denominator differs from the total N as only 15 participants had pre- and post-D3 DSA.

[c] Preexisting positive increase DSA post-D3 denotes that the patient had a positive HLA prior pre-D3 that was increased when measured post-D3.

A1ATD, alpha-1 antitrypsin deficiency; AMT, antimetabolite therapy; BO, bronchiolitis obliterans; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; DSA, donor-specific antibody; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; PH, pulmonary hypertension.