Assessment of Carfilzomib Treatment Response in Lung Transplant Recipients With Antibody-mediated Rejection

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INTRODUCTION

Survival after lung transplant has greatly improved over time. However, long-term outcomes remain challenging with a median survival of 6 y.1 Antibody-mediated rejection (AMR) occurs at a high rate in lung recipients within the first year and is strongly associated with subsequent development of chronic lung allograft dysfunction (CLAD). In 2016, the International Society of Heart and Lung Transplantation (ISHLT) introduced a consensus definition for AMR based on the following criteria: (1) circulating donor-specific antibody (DSA) depletion or conversion to noncomplement-activating antibodies. Herein, we describe our center’s experience treating AMR with CFZ. Methods. All patients treated with CFZ for AMR from 2014 to 2019 were included. The primary outcome was a positive response to CFZ was defined as: (1) loss of DSA C1q-fixing ability after last CFZ dose; (2) clearance of de novo DSA; or (3) decrease in de novo DSA mean fluorescence intensity of >3000. Results. Twenty-eight patients with 31 AMR episodes were treated with CFZ. A positive response was observed in 74.4% of AMR episodes and 82.1% of patients. This response was driven by loss of complement 1q fixation (70.6%), elimination of class I DSAs (78.6%), and reduction in both classes I (median 2815, 79.5% reduction from baseline) and II DSA mean fluorescence intensity (3171, 37.1%). Conclusions. CFZ shows potential for ameliorating AMR; however, additional studies are needed to define optimal time of administration.
2014 and 2019. Patients were excluded if they had received CFZ (before transplantation for desensitization). Treatment of AMR (with PLEX and IVIG) at our institution was not protocolized until 2018. Decision to use CFZ for treatment of AMR in addition to PLEX and IVIG was per clinician discretion. CFZ was dosed at 20 mg/m² over 10–30 min on days 1, 2, 8, 9, 15, and 16 per protocol; however, timing of administration relative to PLEX was not predetermined. Premedication given to all patients included intravenous (IV) fluids, acetaminophen, diphenhydramine, and steroids. Patients also received postfusion IV fluids for mitigation of nephrotoxicity. Acute rejection was diagnosed on transbronchial lung biopsy specimens obtained during routine bronchoscopy at week 2 and months 1, 2, 3, 6, 8, and 12 posttransplantation or when bronchoscopy was performed for clinical indication. As C4d staining has been shown to be poorly reproducible in lung tissue, our institution does not routinely conduct C4d staining.2,4 Instead of C4d staining, our institution conducts complement 1q (C1q) binding assays to assess complement activation potential.1 Posttransplant DSAs were checked at week 1; months 1, 2, 3, 4, 5, 6, 8, and 10 in the first year; every 3 mo after year 1; every 4 mo after year 2; and then biannually after year 3. DSAs may also be ordered for clinical indications.

Data collection and reporting were approved by the Institutional Review Board at the Houston Methodist Research Institute, protocol number PRO00000587.

**Immunosuppression Protocol**

At the time of transplant, all patients received basiliximab for induction per institution protocol (20 mg IV) on postoperative day (POD) 0 and POD 4. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. Tacrolimus dosing was adjusted to maintain a trough level of 10–15 ng/mL for the first 90 d posttransplantation, 8–12 for days 91–365, 5–10 ng/mL for years 1–3, and tapered to 5–8 ng/mL thereafter. Infection prophylaxis included sulfamethoxazole-trimethoprim for lifelong Pneumocystis jirovecii pneumonia; valganciclovir for cytomegalovirus prophylaxis for 12 mo in seropositive recipients and lifelong in mismatched recipients; and voriconazole for fungal prophylaxis for 3 mo.

**Outcomes and Statistical Analysis**

The primary endpoint was a positive response to CFZ therapy as determined by having at least 1 of the following criteria: (1) loss of DSA C1q-fixing ability after the last CFZ dose; (2) clearance of de novo DSA (dnDSA) [mean fluorescence index (MFI) drops below lower limit of detection of 2000]; or (3) a decrease in the dnDSA MFI of >3000 of the immunodominant DSA compared with the baseline pre–CFZ value. The MFI reduction threshold of 3000 was determined by prior studies that demonstrated an increased risk of graft loss with DSA >3000 MFI (range 1000–5000 MFI).4 Given the ability of PLEX to remove antibodies and lower titers independent of other treatment, post–CFZ DSAs to measure response were selected based on first DSAs checked after the last CFZ dose given.

The components of our primary endpoint were selected for the following reasons: (1) we sought to assess CFZ’s effect on a DSA’s propensity to activate complement. We acknowledge the limitations of using C4d (complement was activated) versus C1q (this DSA could activate competent); however, our institution does not conduct C4d staining on the lung tissue; (2) whether the DSA remained detectable versus was eliminated; and (3) if a patient’s DSA was not completely eliminated but a significant reduction was observed, additional therapies would not be administered, but rather, more frequent follow-up monitoring would be employed.

Additionally, we sought to identify variables associated with a positive response to CFZ (CFZ responders) versus lack of response (CFZ nonresponders). If patients experienced >1 episode of AMR, only the first rejection episode was used to classify response. Secondary endpoints included pulmonary function trends, infections within 1 y after the first CFZ dose, and incidence of AKI within 7 d after each CFZ dose. If the same organism was identified on several cultures both before and after CFZ administration, the patient was considered colonized and the infection was not included within the analysis.

Patient characteristics were reported as frequencies and proportions for categorical variables and as median and interquartile range (IQR) for continuous variables. Differences across groups (CFZ responders versus CFZ nonresponders) were determined by Fisher exact tests for categorical variables and the Kruskal–Wallis test for continuous variables. Kaplan–Meier curves were used to depict the patient survival. A change in the DSA MFIs was presented by line plots. Two-way median cubic spline plots were fitted using the Stata’s mspline command to depict the mean change in the forced expiratory volume percent (%FEV1) over time. The mean change in %FEV1 over time was also estimated using the linear mixed model. All analyses were performed on Stata version 16.1 (StataCorp LLC, College Station, TX). A P value of <0.05 was considered as statistically significant.

**RESULTS**

**Patient Characteristics**

Between 2014 and 2019, there were 31 episodes of AMR treated with CFZ in combination with plasmapheresis and IVIG in 28 unique patients. Baseline demographics are depicted in Table 1. Patient AMR episode characteristics and treatment are depicted in Tables 2 and 3, respectively. Allograft dysfunction presented as documented decline in pulmonary function before CFZ administration, inpatient admission for decline in oxygen saturation, radiographic abnormalities, or initiation of mechanical ventilation or noninvasive ventilation. Eight patients received RTX in addition to CFZ; 6 were given RTX before CFZ and 2 after. Nine patients also received antithymocyte globulin (ATG) (1 patient received 2 courses); 7 pre-CFZ and 2 post-CFZ. Details regarding the timeline of patients receiving multiple therapies is provided within supplemental material (Figure S1, SDC, http://links.lww.com/TXD/A315). All patients received between 2 and 5 PLEX sessions and IVIG supplementation.

**DSAs Characteristics and Endpoints**

All patients had class II dnDSAs, with 14 patients (50.0%) also developing class I dnDSAs (Table 2). Most commonly, DQ dnDSAs developed in 25 patients (89.3%), followed by DR in 16 patients (57.1%). Median time to dnDSA was 105 d posttransplantation (IQR 30–573); 18 patients (64.2%) developed dnDSAs within the first year and 8 (32.0%) within 30 d posttransplantation.
Twenty-four of 31 (77.4%) AMR episodes and 23 of 28 patients (82.1%) achieved a positive response to CFZ. This positive response was largely attributed to elimination of DSAs. Of the 14 patients with class I dnDSAs, 11 (78.6%) had complete resolution of DSA after treatment with CFZ. Of the 28 patients with class II dnDSAs, 6 (21.4%) had complete resolution of DSA. Post-CFZ DSAs were checked in all patients at a median of 15.5 d (IQR 7–25) after the last CFZ dose was given [median of 40 d (IQR 26–55) after the last PLEX session]. The median pre-CFZ class I DSA MFI was 3540 (IQR 2378–5490) with a median MFI reduction of 2815 (IQR 2284–4297) (79.5% reduction from baseline) (P < 0.001) (Figure 1). Class II DSA MFIs decreased from a median 8291 (IQR 6875–10 628) to 5120 (IQR 2190–8074) (37.1% reduction from baseline) (P = 0.01). Changes in DSA MFI by the CFZ response group are depicted in Figure 2A and B.

C1q binding was checked in 23 patients and was initially positive in 17 (73.9%). All but 1 of the C1q positive patients had presence of C1q binding checked posttreatment with CFZ; 12 (70.6%) became C1q negative, whereas 4 remained positive (23.5%). C1q binding was not rechecked post-CFZ in the 1 patient because of withdrawal of care. Median pre-CFZ C1q MFI was 21 401 (IQR 13 189–33 364) with a median reduction of 17 968 (IQR 7336–29 270) (84.0% reduction from baseline).

Pulmonary Function

Pulmonary function tests from both pre- and post-CFZ were available for 26 patients. A change in %FEV1 pre- and post-CFZ for the entire cohort is depicted by a spline plot in Figure 3. Given the small sample size, especially in the nonresponder group (n = 5), the spline plot was not stratified by response groups but is provided within the supplemental material (Figure S2, SDC, http://links.lww.com/TXD/A315).

Peak post-CFZ pulmonary function was observed around 12 mo after the last CFZ dose. Using a linear mixed model to estimate the change in %FEV1 over time for longitudinal data, the estimated mean decline in %FEV1 before CFZ administration was found to be −0.75% per month (95% confidence interval −1.29, −0.21). With a median follow-up time of 7 mo before CFZ administration, the median decline in FEV1 was 161 mL from a baseline of 1662 mL (~10% decline in function from baseline) prompting treatment. At time of peak pulmonary function post-CFZ, we observed an estimated FEV1 improvement of 533 mL [a mean increase in %FEV1 of 0.59% per mo (95% confidence interval −0.35, 1.52) compared to nadir function]. The estimated rate of decline in %FEV1 following the CFZ administration was −0.59% per month during a median follow-up time of 6 (range 0–46) mo.

Safety Endpoints

Sixteen patients (57.1%) who received CFZ for AMR died. No patients within this cohort required retransplant. Median time from transplant to death was 2.9 y (IQR 0.9–5.1) and median time from CFZ administration to death was 0.8 y (IQR 0.4–2.0). Causes of death were chronic rejection (n =
Twenty-one (75.0%) patients received the full course (all 6 doses) of CFZ. Patients who did not receive all 6 doses did not complete their courses because of active infections, clinical decompensation, or withdrawal of care. Eight patients (28.5%) developed acute kidney injury (AKI) within 7 d after receiving CFZ; serum creatinine increased by a median of 0.5 mg/dL. All patients achieved renal recovery without intervention.

Positive cultures and febrile episodes within 1 y after CFZ administration were collected and assessed. Fifteen (53.5%) patients experienced a bacterial infection with the most common organisms isolated in respiratory cultures being Pseudomonas aeruginosa and Staphylococcus aureus. These infections occurred at a median of 145 d (IQR 70–169) after administration of the first dose of CFZ. Nine (60%) of the 15 who developed infections [respiratory (n = 4), bacteremia (n = 4), and sinus (n = 1)] received RTX or ATG in addition to CFZ.

CFZ Responders Versus Nonresponders

Patient characteristics thought to be related to response to CFZ were analyzed. These included: class I and class II pre-CFZ DSA MFI, time to development of the first dnDSA posttransplant, time from the development of first dnDSA to treatment with CFZ, inability to receive the full 6 doses of CFZ, dnDSA burden, dnDSA class, and the presence of C1q antibodies before treatment (Table 4). Out of these covariates, a delay of >30 d between DSA development and CFZ initiation was associated with lack of response.

Given the clinical importance of overall graft and patient survival versus laboratory markers of response alone, we further evaluated survival between CFZ responders and nonresponders up to 1-y post–carfilzomib administration (Figure 4). CFZ responders experienced greater 1-y survival posttreatment (78.0% versus 20.0%, \( P = 0.004 \)) compared to nonresponders.

DISCUSSION

This single-center observational case-series found that lung transplant patients with AMR achieved a positive response to carfilzomib as defined by a composite endpoint of loss of DSA C1q-fixing ability, clearance of dnDSA, or decrease in dnDSA MFI of >3000. These results provide impetus for
further research and must be interpreted with several limitations in mind.

Treatment of AMR traditionally involves a combination of modalities to address the varying pathophysiology including plasmapheresis, IVIG, and rituximab. PLEX and use of IVIG predictably remove immunoglobulins from systemic circulation but do not affect the production of antibodies. Rituximab, a chimeric monoclonal IgG antibody directed against CD20, targets naive and memory B cells. However, rituximab-based regimens have not been shown to durably reduce DSA levels, potentially due to the lack of effect on plasma cells surviving within bone marrow.\(^6\) Proteasome inhibitors directly target and deplete plasma cells producing DSAs in addition to reducing preexisting DSA levels.

Data regarding the use of proteasome inhibitors, primarily bortezomib, are widely available in kidney transplantation for both desensitization and treatment of AMR.\(^9\) Studies exploring the benefit of irreversible proteasome inhibition with CFZ have suggested positive findings. The use of proteasome inhibitors in lung transplantation was first described in 5 patients treated with bortezomib for acute rejection, all with positive response.\(^9\) The use of carfilzomib in lung transplantation for treatment of AMR was first described by Ensor et al.\(^3\)

Considering 48% of our patients also received RTX or ATG, with 83.3% (n = 10) of them achieving a positive response, utilization of a multipronged approach for treating AMR targeting both T cells, B cells, and plasma cells may be considered in those with severe dysfunction. Further research examining this approach is recommended with careful consideration given to increased infectious risk.

The positive response achieved by our patients could be overstated when considering the proportion of patients who spontaneously clear their DSAs without any preceding treatment. The human leukocyte antigens antibodies after the lung transplantation study reported that 20% of patients with dnDSAs spontaneously cleared them, all of whom developed their dnDSAs within the first 30 d posttransplant.\(^10\)

### TABLE 3.

| Patient | Concurrent ACR | ISHLT grade | No. PLEX | RTX | ATG | Time from LTxp to first dnDSA (d) | Time from first dnDSA to first CFZ (d) | Positive response to CFZ | Component of primary outcome | Clearance of DSA | Decrease in MFI >3000 | C1q reversed | Time from LTxp to death (y) | Time from first CFZ to death (y) |
|---------|----------------|-------------|-----------|------|-----|-------------------------------|---------------------------------|-------------------------|-----------------------------|----------------|---------------------|-------------|----------------------------|------------------|
| 1       | A2             | 5           | 28        | 26   | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 1.05        | 0.39                      |                  |
| 2       | 5              | 3           | 21        | 176  | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 1.27        | 2.60                      |                  |
| 3       | 5              | 3656        | 17        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 4.08        | 3.19                      |                  |
| 4a      | A1             | 3           | 160       | 108  | Y    | Y                             | Y                               | Y                       | Y                           | Y              | NC                  | 5.98        | 0.41                      |                  |
| 4b      | 3              | 661         |           |      |      | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.54        | 0.31                      |                  |
| 5       | 3              | 55          | 16        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 2.59        | 1.15                      |                  |
| 6       | 5              | 624         | 19        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 3.70        | 2.19                      |                  |
| 7       | 5              | 1145        | 283       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 4.63        | 1.0                       |                  |
| 8       | 4              | 1846        | 601       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.50        | 2.21                      |                  |
| 9       | 5              | 1751        | 269       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.06        | 1.30                      |                  |
| 10      | 4              | 14          | 70        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.54        | 0.31                      |                  |
| 11a     | 5              | 79          | 415       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 2.59        | 1.15                      |                  |
| 11b     | 5              | 5           | 480       |      |      | Y                             | Y                               | Y                       | Y                           | Y              | Y                   | 3.27        | 1.72                      |                  |
| 12      | 2              | 513         | 30        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 3.70        | 2.19                      |                  |
| 13a     | 5              | 512         | 19        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 4.63        | 1.0                       |                  |
| 13b     | 5              | 617         |           | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.50        | 2.21                      |                  |
| 14      | 6              | 1099        | 29        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.50        | 2.21                      |                  |
| 15      | 5              | 27          | 236       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 2.06        | 1.30                      |                  |
| 16      | 3              | 1296        | 14        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 4.63        | 1.0                       |                  |
| 17      | 4              | 28          | 4         | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 4.63        | 1.0                       |                  |
| 18      | 4              | 60          | 18        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.50        | 2.21                      |                  |
| 19      | 3              | 27          | 12        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.50        | 2.21                      |                  |
| 20      | 3              | 105         | 89        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.84        | 0.24                      |                  |
| 21      | 3              | 166         | 58        |      |      | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 1.28        | 0.45                      |                  |
| 22      | 5              | 210         | 94        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 5.51        | 0.50                      |                  |
| 23      | 5              | 1747        | 81        |      |      | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |
| 24      | 5              | 18          | 16        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |
| 25      | 5              | 20          | 66        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |
| 26      | 5              | 30          | 480       | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |
| 27      | A2             | 4           | 7          | 22   | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |
| 28      | 5              | 32          | 21        | Y    | Y    | Y                             | Y                               | Y                       | Y                           | NC             | Y                   | 0.78        | 0.68                      |                  |

*Patients 4, 11, and 13 had 2 episodes of AMR (a and b).

*Before CFZ.

*After CFZ.

AMR, antibody-mediated rejection; ATG, antithymocyte globulin; CFZ, carfilzomib; C1q, complement 1q; dnDSA, de novo DSA; DSA, donor-specific antibody; ISHLT, International Society of Heart and Lung Transplantation; LTxp, lung transplant; MFI, mean fluorescence index; NC, not checked; No, number; RTX, rituximab; Y, yes.
the lung transplantation study was limited to 4 mo posttransplant, thereby limiting the prediction of spontaneous clearance of dnDSAs that develop after this timeframe. Eight of our patients developed DSAs within 30 d posttransplant, 6 of whom achieved a positive response. Of the 6, 3 cleared their DSA, whereas the other responses were driven by both significant reduction in class II MFI and reversal of C1q. From prior institutional data between 2009 and 2013, we determined that one-third of lung transplant recipients with dnDSAs will spontaneously clear without any sequelae compared to those with persistent DSAs; however, this study included all transplant recipients who developed dnDSAs regardless of AMR diagnosis.11 Our study cohort included patients with other markers of AMR present (ie, allograft dysfunction, lung histology, and assessment of complement activation) and still found a majority of patients achieved a positive response.

The potency of DSA MFI reduction on class I versus class II DSAs remains an interesting phenomenon. Philogene et al12 reported a decrease in class I DSA MFI by 32% and an increase in class II DSA MFI by 29% in 13 kidney transplant patients receiving bortezomib for desensitization. Khuu et al13 assessed DSA MFI depletion characteristics in 9 heart transplant recipients with AMR treated with bortezomib and found class I DSA MFI reduction of 50% compared to only 3% class II DSA MFI. Our class II DSA MFI reduction was not as profound as what Ensor et al3 reported (26% versus 80%); however, our results remain consistent with prior literature: we found reduction in both class I and II DSA MFI, but the response was more profound with class I DSAs. Although interpretation of MFI reduction alone is limited (differing institutional thresholds, assay sensitivities, and potential for IVIG interference), longitudinal trends and potency of reduction coupled with clinical status can be useful.

Within the kidney transplantation literature, class I DSAs are more commonly associated with early AMR, and class II with late AMR and graft failure.14 Within lung transplantation, class II DSAs—specifically DQ—have been associated with the development of CLAD. The more robust decrease in class I DSA MFI observed could be attributed to the innate differences in class I (potential to be transient) versus class II DSAs (more likely to be persistent), rather than the direct effect of CFZ.

Several studies have reported that persistent DSAs are associated with increased risk of chronic rejection and mortality.15-18 Persistent DSAs have been defined as presence of HLA antibodies directed against the same donor HLA locus on at least 2 separate measurements at least 3 wk apart. However, the classification of persistence does not consistently include those treated with IVIG or RTX.10,11,16,19 Our analysis of CFZ nonresponders versus responders supports the idea of early...
AMR therapy to prevent persistence of dnDSAs and subsequent poor outcomes. The challenge of determining those who may spontaneously clear their dnDSAs, and establishing a threshold for the maximum allowable time between detection of a dnDSA and initiation of AMR treatment remain. This time frame could also correlate with the progression of B cells into plasma cells.

An important factor determining AMR outcomes is the concept of “early” versus “late” AMR. The main hindrance of this designation is determining when AMR first appears. We evaluated time from transplant to first dnDSA, time from first dnDSA to CFZ (as a continuous variable), and time from first dnDSA to CFZ >30 d in attempt to better classify “early” versus “late” response. Within our entire cohort, median time from transplant to CFZ was 266 d (IQR 76–764)—suggesting later AMR; however, this does not factor in use of CFZ as a “last line” option to an early AMR episode.

Although the overall length of posttreatment survival in our cohort is discouraging (2.9 y from time of transplant and 0.8 y from CFZ administration), it is important to note changes in practice that occurred through the course of our

### FIGURE 3.
Spline plot for change in percent forced expiratory volume in 1 s (%FEV1) over time, all patients. Change in %FEV1 for all patients within the cohort is depicted in relation to time of carfilzomib administration. Before carfilzomib administration, the slope of decline in FEV1 was −0.75% per mo. Peak function postcarfilzomib was observed at 12 mo postdose. The slope of decline in FEV1 after carfilzomib administration was −0.59% per mo.

### TABLE 4.
Characteristics of CFZ nonresponders vs responders

|                            | CFZ nonresponders (n = 5) | CFZ responders (n = 23) | P    |
|-----------------------------|---------------------------|------------------------|------|
| No. PLEX, median (IQR)      | 5.0 (4.0, 5.0)            | 4.0 (3.0, 5.0)         | 0.54 |
| RTX, n (%)                  | 1 (20.0)                  | 6 (27.3)               | 1.00 |
| ATG, n (%)                  | 1 (20.0)                  | 8 (34.8)               | 1.00 |
| Pre-CFZ class I DSA MFI, median (IQR) | 3527.0 (2268.0, 5490.0) | 3553.0 (2378.0, 6304.0) | 0.70 |
| Post-CFZ class I DSA MFI, median (IQR) | 2349.0 (2277.0, 3235.0) | 0.0 (0.0, 0.0)         | <0.001 |
| Change in class I MFI, median (IQR) | −1178.0 (−2255.0, 9.0) | −3553.0 (−6304.0, −2378.0) | 0.02 |
| Sig change in class I MFI, n (%) | 0 (0.0)                   | 7 (30.4)               | 0.29 |
| Pre-CFZ class II DSA MFI, median (IQR) | 6356.5 (5231.0, 9356.0) | 8525.5 (7166.0, 10628.0) | 0.26 |
| Post-CFZ class II DSA MFI, median (IQR) | 5004.5 (3882.5, 9880.8) | 5830.0 (2157.0, 8074.0) | 0.62 |
| Change in class II MFI, median (IQR) | 1413.0 (557.0, 8201.0) | 1889.0 (−2508.0, 3893.0) | 0.74 |
| Sig change in class II MFI, n (%) | 0 (0.0)                   | 16 (69.6)              | 0.01 |
| Time from LTxP to first DSA (d), median (IQR) | 166.0 (21.0, 1747.0) | 93.0 (28.0, 624.0) | 0.88 |
| Time from first DSA to CFZ (d), median (IQR) | 81.0 (70.1, 175.8) | 26.4 (16.8, 108.4) | 0.16 |
| Time from first DSA to CFZ >30 d, n (%) | 5 (100.0)                 | 9 (39.1)               | 0.04 |
| Patients not receiving full course, n (%) | 3 (60.0)                  | 4 (17.4)               | 0.08 |
| No. DSA, median (IQR)       | 3.0 (1.0, 6.0)            | 3.0 (3.0, 4.0)         | 0.69 |
| No. DSAs, n (%)             | 3 (60.0)                  | 18 (78.3)              | 0.57 |
| <5                          | 2 (40.0)                  | 5 (21.7)               | 0.61 |
| ≥5                          | 2 (40.0)                  | 5 (21.7)               | 0.57 |
| Class of DSA, n (%)         | 0.61                      | 0.57                   | 0.61 |
| A                           | 2 (40.0)                  | 5 (21.7)               | 0.57 |
| B                           | 2 (40.0)                  | 5 (21.7)               | 0.57 |
| C                           | 1 (20.0)                  | 2 (8.7)                | 0.46 |
| DR                          | 3 (60.0)                  | 13 (56.5)              | 1.00 |
| DQ                          | 4 (80.0)                  | 21 (91.3)              | 0.46 |
| DP                          | 3 (60.0)                  | 9 (39.1)               | 0.62 |
| DSAs eliminated, n (%)      | 0 (0.0)                   | 13 (56.5)              | 0.04 |
| C1q pos, n (%)              | 2 (86.7)                  | 15 (75.0)              | 1.00 |
| Loss of C1q positivity, n (%) | 0 (0.0)                  | 12 (60.0)              | 0.19 |
| Death, n (%)                | 4 (80.0)                  | 12 (52.2)              | 0.36 |
| Time from LTxP to death (y), median (IQR) | 3.3 (0.8, 5.7) | 2.9 (1.1, 4.4) | 0.81 |
| Time from CFZ to death (y), median (IQR) | 0.4 (0.4, 0.5) | 1.2 (0.6, 2.3) | 0.07 |

Bolded values were those that were statistically significant (ie, p<0.05).

*CFZ positive response classification in this table is based on the first episode of AMR.

*Either pre- or post-CFZ administration.

AMR, antibody-mediated rejection; ATG, antithymocyte globulin; CFZ, carfilzomib; C1q, complement 1q; dnDSA, de novo DSA; DSA, donor-specific antibody; IQR, interquartile range; LTxP, lung transplant; MFI, mean fluorescent intensity; No. PLEX, number of plasmapheresis sessions; RTX, rituximab.
of these positive results to CFZ alone, and thus, our results should be interpreted accordingly. The limited sample size affects our ability to comprehensively draw conclusions about key differences between CFZ responders and nonresponders. Last, given the known role AMR may play in CLAD onset/progression, it is important to note that we did not assess our patients for restrictive (R-CLAD or RAS) or bronchiolitis obliterans designations. Application of the calculated decline in %FEV1 observed in our cohort must be evaluated accordingly.

Our cohort is the largest describing use of CFZ for the treatment of AMR in lung transplant recipients to date. The positive response that a majority of our patients experienced was determined by a decrease in both class I and II DSA MFI, elimination of dnDSAs, and reversal of C1q positivity. Although more than half of our cohort died within 2 y of CFZ administration, responders still experienced a far better 1 y survival benefit compared to nonresponders. This survival benefit would need to be considered alongside the projected mortality of untreated AMR and subsequent development of CLAD. Larger prospective interventional studies investigating the ideal time from dnDSA development to initiating AMR treatment, and defining the most appropriate time to utilize CFZ are needed.

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