OPEN

Lung Transplant Outcomes in Adults in the United States: Retrospective Cohort Study Using Real-world Evidence from the SRTR

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Background. The Scientific Registry of Transplant Recipients was retrospectively analyzed to provide real-world evidence of the efficacy and safety of tacrolimus-based immunosuppressive regimens in adult lung transplant recipients in the United States. **Methods.** Adult recipients (N = 25 355; ≥18 y) of a primary deceased-donor lung transplant between January 1, 1999, and December 31, 2017, were followed for 3 y posttransplant based on immunosuppressive regimen at discharge: immediate-release tacrolimus (TAC) + mycophenolate mofetil (MMF), TAC + azathioprine (AZA), cyclosporine (CsA) + MMF, or CsA + AZA. The primary outcome was the composite endpoint of graft failure or death (all-cause) at 1 y posttransplant (calculated via a modified Kaplan–Meier method). **Results.** Discharge immunosuppressive regimens in lung transplant recipients changed over time, with a substantial increase in the use of TAC + MMF. TAC + MMF was the most common immunosuppressive regimen (received by 61.0% of individuals at discharge). The cumulative incidence of graft failure or death at 1 y posttransplant in adult lung transplant patients receiving TAC + MMF was 8.6% (95% confidence interval 8.1-9.1). Risk of graft failure or death was significantly higher in adults receiving CsA + MMF or CsA + AZA compared with TAC + MMF, with no significant difference seen between TAC + MMF and TAC + AZA. TAC + MMF had the highest continued use at 1 y posttransplant (72.0% versus 35.4%–51.5% for the other regimens). There was no increase in the rate of infection or malignancy in the TAC + MMF group. **Conclusions.** Real-world evidence from the most comprehensive database of transplant recipients in the United States supports the use of TAC in combination with MMF or AZA as maintenance immunosuppression in adult lung transplant recipients.

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INTRODUCTION

Lung transplantation is an important option for the management of individuals with chronic, end-stage respiratory disease.[1-3] Over 4600 lung transplants are performed worldwide annually, 55% of which are performed in North America.[3] Tacrolimus is a calcineurin inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients of allogeneic liver, kidney, or heart transplants, in combination with other immunosuppressants.[4] Although protocols may vary between centers, lung transplant recipients generally receive maintenance immunosuppression with immediate-release tacrolimus (TAC) or cyclosporine A (CsA) in combination with mycophenolate mofetil (MMF) or azathioprine (AZA) and steroids.[3,5-7] In the United States, TAC + MMF is used in 85.5% of lung transplant recipients 12 y of age or older.[7]

A limited number of small randomized trials have compared TAC- and CsA-based immunosuppressive regimens in adult lung transplant recipients.[8-12] Results of these studies have been included in 2 separate meta-analyses, both of which concluded that using TAC as a primary immunosuppressant for lung transplant recipients resulted in comparable reduction in acute rejection episodes compared with CsA.[13,14]

This analysis of the Scientific Registry of Transplant Recipients (SRTR) database was undertaken to provide real-world evidence of the effectiveness and safety of TAC-based immunosuppressive regimens in adult lung transplant recipients in the United States, in support of an application to expand the FDA-approved indications of TAC to include lung transplantation.

MATERIALS AND METHODS

This retrospective cohort study evaluated transplant-related outcomes and use of TAC and other immunosuppressive agents over time in adult lung transplant recipients in the SRTR. The SRTR is a national transplant registry containing data on all lung transplant candidates, recipients, and donors in the United States from October 1987 onwards.[15] Data are collected at the time of discharge posttransplantation and annually thereafter. The registry is linked to other sources, including the Centers for Medicare & Medicaid Services and the National Technical Information Service's Death Master File, to augment collection of death data. The SRTR is made available under a Data Use Agreement to external researchers. No Institutional Review Board, Independent Ethics Committee, or Competent Authority approval was required for this analysis.

Adult (≥18 y) recipients of a primary, deceased-donor, single- or double-lung transplant between January 1, 1999 and December 31, 2017 were followed for 3 y posttransplant. Exclusion criteria were: any previous organ transplant; multiorgan or living-donor organ transplant; death during the index hospitalization; graft failure before discharge (including retransplantation during the index hospitalization); discharge date missing or >1 y posttransplant; and missing data about maintenance immunosuppressive regimen at discharge.

Outcomes

The primary outcome was the cumulative incidence of the composite endpoint of graft failure or death (due to any cause) within 1 y (365 d) posttransplant. Secondary outcomes included the proportion of transplant recipients who remained on their discharge immunosuppressive regimen at 1 y posttransplant, the 3-y posttransplant incidence of the primary endpoint, and the 1- and 3-y posttransplant incidence of recipient death, graft failure, any rejection, bronchiolitis obliterans syndrome (BOS), and the composite endpoint of graft failure, death, or any rejection. Safety was assessed at 1 and 3 y posttransplant; endpoints were the incidence of overall malignancy (excluding non-melanoma skin cancers), posttransplant lymphoproliferative disease (PTLD), hospitalization for infection, new-onset diabetes after transplant (NODAT), and renal dysfunction (defined as need for chronic dialysis, or renal transplant, or estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2 [estimated using the Chronic Kidney Disease Epidemiology Collaboration equation[16]]).

Statistical Analyses

All eligible adult lung transplant recipients from the SRTR were included in the analysis. Results were evaluated using descriptive analyses, and no *a priori* hypothesis for statistical testing was defined. Analyses used an intent-to-treat approach based on immunosuppressive regimen at hospital discharge: TAC + MMF, TAC + AZA, CsA + MMF, or CsA + AZA.

Trends in transplant-related factors were assessed over time. Three time periods were evaluated (1999–2005, 2006–2009, 2010–2017), based on the following transplant care milestones: (1) introduction of the lung allocation score (LAS) in 2006; (2) FDA approval of TAC + MMF for kidney transplantation in 2009; and (3) availability of generic tacrolimus from 2009. Variables evaluated for change in frequency included diagnosis, age at transplant, lung transplant procedure, lung total ischemia time, LAS at transplant, donor age group, and use of induction therapy (any, T-cell– depleting agents, or interleukin-2 [IL-2] antagonists).

The cumulative 1-y incidence of both the primary composite endpoint and death were estimated as 100% minus the Kaplan–Meier survival probability for the total cohort and each exposure group. Because immunosuppressive regimen is recorded at hospital discharge, observation began at the discharge date (left truncation) and ended at the minimum of the event date, the end of 2018, 365 d (1 y) posttransplant or loss to follow-up (right censoring). Four individuals in the TAC + MMF group were discharged and then experienced an event by day 7 posttransplant. Few others had been discharged by this time so the number at risk was small, which had an outsized effect on the point estimate and 95% confidence intervals (CIs). The analysis by exposure group was therefore repeated after reassigning these 4 events to day 10 posttransplant (ie, the earliest event day for any other regimen). Incidence estimates from this modified analysis were the primary focus for interpretation. Apart from reassigning the event day of the 4 individuals with an early event, all analyses were carried out according to the *a priori* plan. Sensitivity analyses were undertaken that indexed transplant recipients at hospital discharge and in which any individual lost to follow-up was assumed to have experienced the event.

The Aalen–Johansen competing risk estimate of cumulative incidence was presented for graft failure, overall malignancy, and PTLD. For graft failure, death for causes

not attributable to graft failure was the competing risk; for overall malignancy and PTLD, death or graft failure was the competing risk. For other secondary endpoints, data were collected at intervals without event dates. Cumulative incidence percentages for 1 and 3 y posttransplant were computed as: (number of individuals with an event during the time-interval)/(number of individuals at baseline).

Hazard ratios for the risk of graft failure or death for other immunosuppressive regimens versus TAC + MMF were estimated using Cox proportional hazards models with or without adjustment for potential confounding covariates. The covariates for adjustment were selected using regression models to predict exposure group based on baseline characteristics. Cox proportional hazards models were also used to test for baseline characteristics associated with a greater risk of graft failure or death.

Analyses were conducted using RStudio 1.4.1103 and R version 4.0.0[17]; *P* values < *0.05* were considered statistically significant.

RESULTS

Transplant Recipient Population

A total of 28 817 adults received a lung transplant between 1999 and 2017. Of these, 25 355 met the inclusion criteria for this analysis (Figure 1). The most common reasons for exclusion were death, graft failure, or retransplantation before discharge (n = 1767 [6.1%]), previous transplant (lung or otherwise; n = 1174 [4.1%]), and missing maintenance immunosuppression data at discharge (n = 941 [3.3%]). As shown in Table 1, lung transplant recipients were mostly white (89.7%), male (57.3%), and 50–64 y of age (52.3%). Most had received a double-lung transplant (63.9%). Median duration of hospitalization posttransplant was 15 d (interquartile range, 11–25 d). The majority received antibody induction (74.4%), most commonly IL-2 receptor antagonists (used by 44.9% of all lung transplant recipients).

Immunosuppressive Therapy at Discharge

TAC and MMF were the most common nonsteroidal immunosuppressive agents reported at hospital discharge (received by 84.1% and 65.1% of transplant recipients, respectively). TAC + MMF was the most common discharge immunosuppressive regimen (61.0%) (Table 1). As expected, immunosuppressive regimens changed over the analysis period, with use of TAC + MMF increasing and use of CsA and AZA decreasing (Figure 2). In 2010–2017, 78.8% of lung transplant recipients (11 076 of 14 047) received TAC + MMF at hospital discharge.

Lung Transplant Trends Over Time

The number of lung transplants performed annually increased from 692 in 1999 to 2206 in 2017. Overall, 55.4% of lung transplants were performed in 2010–2017 (Table 1). Other notable trends over the analysis period are summarized in **Figure S1, SDC,** http://links.lww.com/TP/C316. Increases were observed in the proportion of transplant recipients with pulmonary fibrosis as the primary cause of lung disease

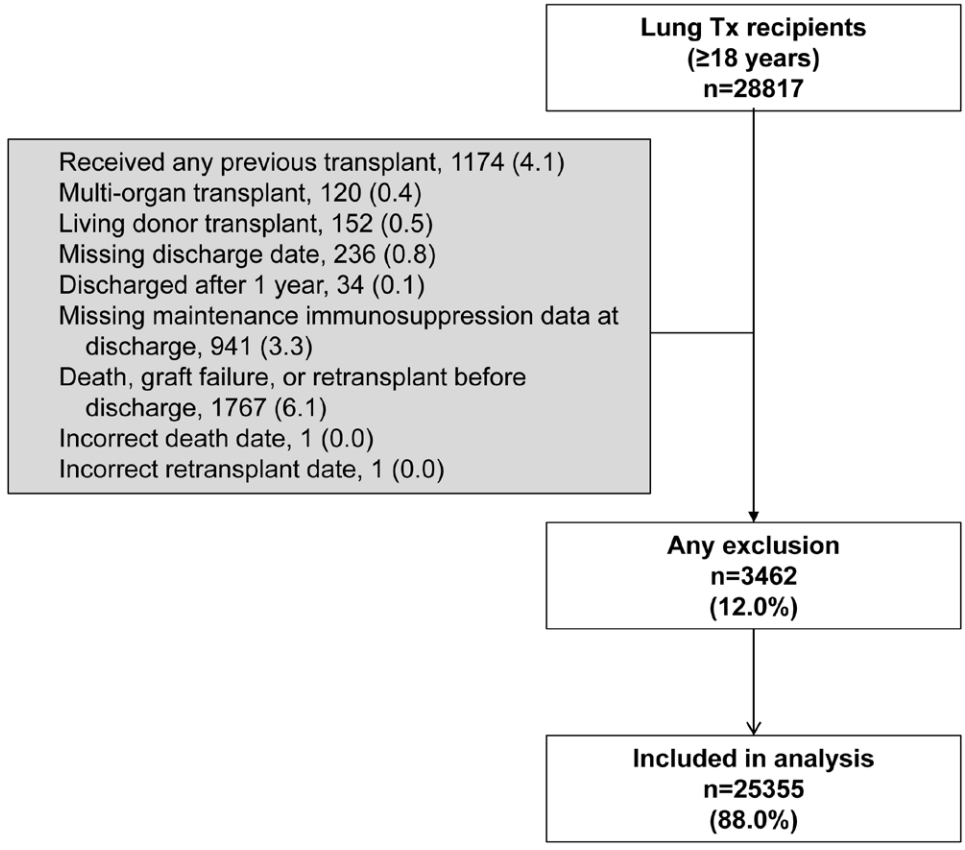

FIGURE 1. Transplant recipient flow chart. Individuals may have been excluded for >1 reason; therefore, the sum of all noncumulative exclusions exceeds the total number of excluded individuals. Tx, transplant.

TABLE 1.

Lung transplant recipient demographics and baseline clinical characteristics

	Total cohort, N = 25 355	TAC + MMF, n = 15 478 (61.0%)	TAC + AZA, n = 4263 (16.8%)	CsA + MMF, n = 1219 (4.8%)	CsA + AZA, n = 1959 (7.7%)
Age at Tx, y	58 (49, 64)	59 (50, 65)	57 (47, 62)	56 (48, 62)	55 (45, 60)
Male, n (%)	14 526 (57.3)	9055 (58.5)	2408 (56.5)	677 (55.5)	1052 (53.7)
Race, n (%)					
White	22 745 (89.7)	13 825 (89.3)	3779 (88.6)	1101 (90.3)	1821 (93.0)
Black	2101 (8.3)	1286 (8.3)	416 (9.8)	106 (8.7)	115 (5.9)
Asian	349 (1.4)	264 (1.7)	46 (1.1)	7 (0.6)	6 (0.3)
Other[a]	160 (0.6)	103 (0.7)	22 (0.5)	5 (0.4)	17 (0.9)
BMI, kg/m^2	25 (21.3, 28.4)	25.4 (21.6, 28.7)	24.5 (20.9, 27.7)	24.3 (20.7, 28.0)	23.6 (20.2, 27.1)
Primary cause of lung disease, n (%)					
Pulmonary fibrosis	11 621 (45.8)	7900 (51.0)	1755 (41.2)	431 (35.4)	477 (24.3)
COPD	9529 (37.6)	5092 (32.9)	1743 (40.9)	621 (50.9)	1102 (56.3)
Cystic fibrosis	3198 (12.6)	1890 (12.2)	595 (14.0)	125 (10.3)	300 (15.3)
Pulmonary hypertension	966 (3.8)	593 (3.8)	163 (3.8)	35 (2.9)	66 (3.4)
Unknown	41 (0.2)	3 (0.0)	7 (0.2)	7 (0.6)	14 (0.7)
LAS at Tx	39.9 (34.7, 50.5)	40 (34.8, 50.9)	39.4 (34.5, 48.6)	39.5 (34.7, 53.1)	38.2 (34.2, 44.5)
Double lung Tx, n (%)	16 190 (63.9)	10 278 (66.4)	2775 (65.1)	558 (45.8)	1011 (51.6)
Year of Tx, n (%)					
1999–2005	6284 (24.8)	1664 (10.8)	1427 (33.5)	861 (70.6)	1494 (76.3)
2006–2009	5024 (19.8)	2738 (17.7)	1305 (30.6)	168 (13.8)	259 (13.2)
2010–2017	14 047 (55.4)	11 076 (71.6)	1531 (35.9)	190 (15.6)	206 (10.5)
Duration of hospitalization post-Tx, d	15 (11, 25)	16 (11, 25)	14 (10, 21)	17 (11, 28)	13 (9, 20)
Induction therapy, n (%)	18 863 (74.4)	12 287 (79.4)	2949 (69.2)	859 (70.5)	1226 (62.6)
T-cell–depleting agents	3444 (13.6)	2224 (14.4)	327 (7.7)	124 (10.2)	271 (13.8)
IL-2 receptor antagonists	11 397 (44.9)	8043 (52.0)	2000 (46.9)	380 (31.2)	309 (15.8)
Donor age, y	32 (21, 46)	33 (22, 46)	30 (21, 44)	29 (20, 43)	28 (20, 43)
Donor male, n (%)	15 327 (60.4)	9391 (60.7)	2574 (60.4)	734 (60.2)	1227 (62.6)
Donor race, n (%)					
White	19 866 (78.4)	12 035 (77.8)	3243 (76.1)	989 (81.1)	1662 (84.8)
Black	4621 (18.2)	2830 (18.3)	900 (21.1)	202 (16.6)	262 (13.4)
Asian	652 (2.6)	458 (3.0)	95 (2.2)	19 (1.6)	26 (1.3)
Other[a]	216 (0.9)	155 (1.0)	25 (0.6)	9 (0.7)	9 (0.5)

Data are median (q1, q3) unless otherwise indicated.
Total cohort column includes data for the 2436 individuals who received immunosuppressive regimens other than the 4 combinations of interest (with or without steroids).
[a]Includes multiracial, native American, and Pacific islander (unknown for 1 transplant recipient in the total cohort).
AZA, azathioprine; BMI, body mass index; CsA, cyclosporine A; COPD, chronic obstructive pulmonary disease; IL-2, interleukin-2; LAS, lung allocation score; MMF, mycophenolate mofetil; TAC, immediate-release tacrolimus; Tx, transplant.

(27.0% in 1999–2005 and 54.5% in 2010–2017), the proportion of transplant recipients ≥65 y of age (6.2% and 30.1% over the 2 time periods, respectively), and the proportion of double-lung transplants (48.6% and 70.4%, respectively). Use of induction therapy and IL-2 receptor antagonists increased (from 67.9% to 78.0%, and from 28.5% to 53.6%, respectively). There was also a trend towards longer lung ischemia times (ischemia time ≥6 h, 17.0% in 1999–2005 and 27.6% in 2010–2017). No obvious temporal trends were observed for LAS at transplant or donor age group (**Figure S1, SDC,** http://links.lww.com/TP/C316).

Efficacy

At 1 y posttransplant, the cumulative incidence of the primary endpoint of death or graft failure in adult lung transplant recipients was 12.9% (95% CI 9.5-16.2) (22.1% [95% CI 19.0-25.1] and 30.1% [95% CI 27.3-32.8] at 2 and 3 y posttransplant, respectively). Improvement in the primary endpoint was observed over time, with cumulative incidence at 1 y decreasing from 16.8% (95% CI 7.9-24.8) in 1999–2005 to 11.7% (95% CI 9.3-14.0) in 2006–2009 and 12.3% (95% CI 6.3-17.9) in 2010–2017. Improvement over time was also observed for the primary endpoint at 3 y posttransplant (34.2% [95% CI 27.1-40.6] in 1999–2005, 30.0% [95% CI 27.9-32.1] in 2006–2009, and 28.7% [95% CI 23.8–33.3] in 2010–2017). It should be noted that the analysis for the total cohort was not modified to account for the 4 early events in the TAC + MMF group and therefore cannot be directly compared with the results of the by-treatment analysis below.

Kaplan–Meier estimates of the cumulative incidence of the primary endpoint (death or graft failure) by discharge immunosuppressive regimen and of graft survival are shown in Figure 3. In the TAC + MMF group, cumulative incidence of graft failure or death was 8.6% (95% CI 8.1-9.1)

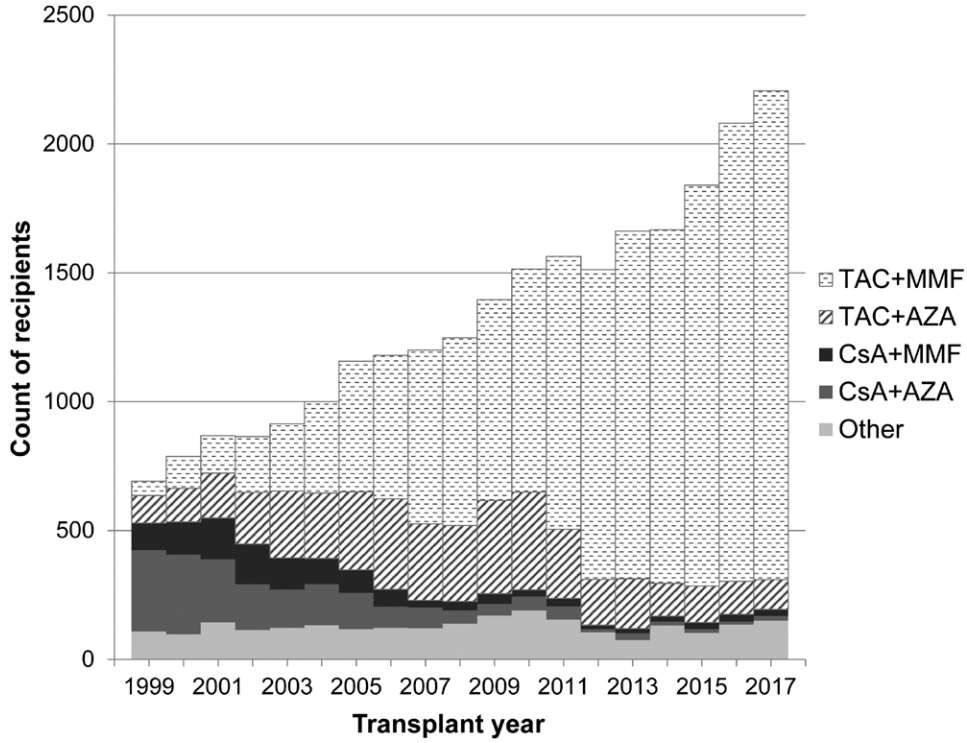

FIGURE 2. Proportion of lung transplant recipients by transplant year and immunosuppressive regimen at hospital discharge. AZA, azathioprine; CsA, cyclosporine A; MMF, mycophenolate mofetil; TAC, immediate-release tacrolimus.

at 1 y posttransplant, 17.6% (95% CI 17.0-18.3) at 2 y, and 26.0% (95% CI 25.2-26.7) at 3 y (Table 2). The rates of the primary endpoint were similar at 1 and 3 y posttransplant in the TAC + MMF and TAC + AZA groups (Table 2). Sensitivity analysis that indexed transplant recipients at hospital discharge provided similar estimates across immunosuppressive regimens (cumulative incidence of the primary endpoint in the TAC + MMF group at 1 y post-discharge, 9.1% [95% CI 8.6-9.5]).

In the TAC + MMF group, graft survival was highest in the most recent time period evaluated. Graft survival at 1 y posttransplant was 88.3% in 1999–2005 versus 92.4% in 2010–2017 in the TAC + MMF group (**Table S1, SDC,** http://links.lww.com/TP/C316) and was 70.1% in 1995–2005 and 75.8% in 2010–2017 at 3 y posttransplant (**Table S2, SDC,** http://links.lww.com/TP/C316).

TAC + MMF had the highest continued use at 1 y posttransplant (72.0% [10 118/14 050] versus 35.4%–51.5% for the other regimens). In transplant recipients who changed regimen in the TAC + AZA group, AZA was most commonly substituted by MMF (21.3% [821/3860]). Individuals receiving CsA-based regimens most commonly switched to TAC; CsA + MMF and CsA + AZA groups were switched to TAC + MMF (23.0% [239/1037] and 10.4% [177/1709], respectively) and TAC + AZA (2.7% [28/1037] and 19.5% [333/1709], respectively) groups at 1 y posttransplant.

In the TAC + MMF group, cumulative incidences of all secondary transplant-related outcomes were similar to or lower than those in the other groups at all time points (**Table 2**). At 1 y posttransplant, the cumulative incidence of any rejection was 25.3% in the TAC + MMF group and 31.3%–49.4% in the other groups. At 3 y posttransplant, the cumulative incidence of any rejection was 36.6% in the TAC + MMF group and 41.9%–59.3% in the other groups. The incidence of the composite endpoint of death, graft failure, or any rejection at 3 y posttransplant was 52.0% in the TAC + MMF group and 56.0%–71.3% in the other groups. The incidence of BOS was 7.1% in the TAC + MMF group and 7.7%–10.2% in the other groups at 1 y posttransplant, and 27.4% and 26.3%–30.7% at 3 y, respectively.

Factors Associated With Graft Failure or Death

As shown in **Table 3**, both with and without adjustment for covariates, the risk of graft failure or death at 1 y posttransplant was significantly higher in the CsA + MMF and CsA + AZA groups than in the TAC + MMF group (with adjustment for covariates, $P < 0.004$ and $P < 0.014$, respectively). Differences between these groups were largely driven by differences in the number of deaths, as graft failure rates were similar across all groups. No significant differences in the risk of graft failure or death were seen between TAC + AZA and TAC + MMF (with adjustment for covariates, $P = 0.716$).

Factors associated with greater risk of graft failure or death in adult lung transplant patients receiving TAC + MMF included recipient age ≥65 y, single-lung transplant, hospital stay >24 d, body mass index <18.5 kg/m^2, serum creatinine ≥1.0 mg/dL, donor age ≥55 y, and donor race (black). These same factors were also associated with greater risk of graft failure or death in one or both CsA groups (**Table S3, SDC,** http://links.lww.com/TP/C316). Factors associated with lower risk of graft failure or death in adult lung transplant patients receiving TAC + MMF were recipient age 35–49 y, recipient race (black), hospital stay ≤14 d, and donor cytomegalovirus-negative.

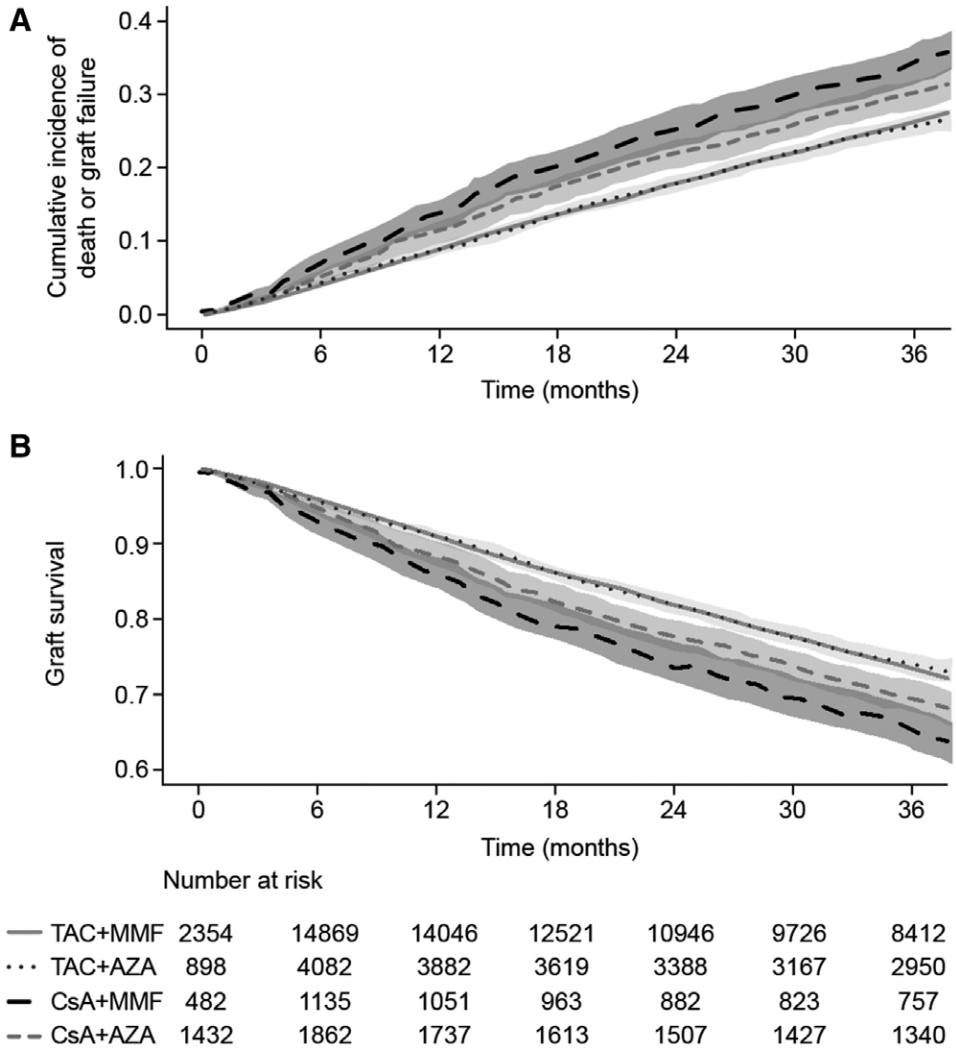

FIGURE 3. Kaplan–Meier estimates of (A) cumulative incidence of death or graft failure and (B) graft survival in lung transplant recipients by immunosuppressive regimen. The time-to-event analysis was left-truncated at the discharge date because inclusion in the study required survival with graft function until discharge; transplant recipients were not at risk for the primary endpoint during hospitalization. As 4 events occurred <10 d posttransplant, the time to event for these 4 transplant recipients (all in the TAC + MMF group) was shifted to 10 d posttransplant. AZA, azathioprine; CsA, cyclosporine A; MMF, mycophenolate mofetil; TAC, immediate-release tacrolimus.

Safety

The most common safety outcome posttransplant was hospitalization for infection in all groups (**Table 4**). In the first year posttransplant, 15.0% of transplant recipients developed renal complications and 16.6% developed NODAT; at 3 y posttransplant, respective incidences were 31.3% and 24.7%. The overall incidence of malignancy was 1.8% at 1 y posttransplant and 5.1% at 3 y. The incidence of renal dysfunction was numerically lower in the TAC + MMF group than in the other immunosuppression groups (11.9% versus 18.8%–25.1% at 1 y posttransplant, and 25.6% versus 37.0%–47.7% at 3 y). For other safety endpoints, incidences in the TAC + MMF group were similar to or lower than those in the other groups at both time points (Table 4).

DISCUSSION

The real-world evidence generated by this retrospective analysis of data from the most comprehensive transplant database in the United States supports the use of TAC + MMF as maintenance immunosuppression in adult lung transplant recipients. As expected, discharge immunosuppressive regimens changed over the analysis period, with a substantial increase in the use of TAC + MMF after 2010. During 2010–2017, approximately 79% of adult lung transplant patients received TAC + MMF as their maintenance immunosuppressive regimen at hospital discharge.

Improvement in lung transplant outcomes was seen over time. Overall 1-y graft survival rates in adult lung transplant patients receiving TAC-based regimens in this analysis are similar to those currently reported in liver and heart transplant recipients.[18] Adult lung transplant patients receiving TAC + MMF had a cumulative incidence of graft failure or death at 1 y posttransplant of 8.6% (or equivalently, graft survival of 91.4%) and had the lowest rejection rates without increased risks of infection or malignancy. No statistically significant differences were seen between the TAC + MMF and TAC + AZA groups in risk of graft failure or death. However, risk of graft failure or death was significantly greater in adults receiving CsA + MMF or CsA + AZA compared with TAC + MMF. This statistically significant result could be considered particularly noteworthy due

TABLE 2.

Transplant outcomes in adult lung transplant recipients by immunosuppressive regimen at hospital discharge

	TAC + MMF			TAC + AZA			CsA + MMF			CsA + AZA		
Outcome	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)
1 y posttransplant												
Death or graft failure[a]	15 478	1272	8.6 (8.1, 9.1)	4263	365	8.8 (7.9, 9.6)	1219	162	13.7 (11.7, 15.7)	1959	217	11.2 (9.8, 12.6)
Death[a]	15 478	1229	8.3 (7.8, 8.7)	4263	346	8.3 (7.4, 9.1)	1219	158	13.4 (11.4, 15.3)	1959	212	11.0 (9.6, 12.4)
Graft failure[b]	15 478	372	2.5 (2.2, 2.8)	4263	110	2.7 (2.2, 3.2)	1219	24	2.0 (1.3, 3.0)	1959	50	2.6 (2.0, 3.4)
Any rejection	15 478	3918	25.3 (24.6, 26.0)	4263	1333	31.3 (29.9, 32.7)	1219	460	37.7 (35.0, 40.5)	1959	968	49.4 (47.2, 51.6)
BOS	15 478	1098	7.1 (6.7, 7.5)	4263	330	7.7 (6.9, 8.5)	1219	95	7.8 (6.3, 9.3)	1959	199	10.2 (8.8, 11.5)
Change in IS regimen	14 050	3932	28.0	3860	1871	48.5	1037	505	48.7	1709	1104	64.6
3 y posttransplant												
Death or graft failure[a]	10 946	1036	26.0 (25.2, 26.7)	3388	315	25.5 (24.1, 26.8)	882	101	34.2 (31.4, 36.8)	1507	153	30.0 (28.0,32.0)
Death[a]	11 278	1012	24.8 (24.0, 25.5)	3465	301	23.9 (22.6, 25.2)	903	101	33.2 (30.5, 35.9)	1528	150	29.0 (27.0, 31.0)
Graft failure[b]	10 946	497	10.6 (10.0, 11.1)	3388	146	10.7 (9.8, 11.7)	882	37	9.0 (7.5, 10.8)	1507	59	9.6 (8.4, 11.0)
Any rejection	11 804	4318	36.6 (35.8, 37.3)	4019	1685	41.9 (40.4, 43.4)	1166	538	46.1 (43.3, 48.9)	1928	1143	59.3 (57.1, 61.5)
BOS	11 804	3232	27.4 (26.7, 28.1)	4019	1195	29.7 (28.4, 31.1)	1166	307	26.3 (23.9, 28.8)	1928	591	30.7 (28.6, 32.7)
Death, graft failure or any rejection	11 804	6143	52.0 (51.3, 52.8)	4019	2250	56.0 (54.5, 57.5)	1166	743	63.7 (61.0, 66.4)	1928	1374	71.3 (69.3, 73.3)

For these outcomes, the time-to-event analysis was left-truncated at the discharge date because inclusion in the study required survival with graft function until discharge; transplant recipients were not at risk for the primary endpoint during hospitalization. As 4 events occurred <10 d posttransplant, the time to event for these 4 transplant recipients (all in the TAC + MMF group) was shifted to 10 d posttransplant. For year 1, the number at risk was all recipients; for year 3, the number at risk was the number at the earliest event in the year and the number of events was the total number of events over the year.

Unless otherwise stated, outcomes are expressed as percentages, calculated as the number of events over the time period of interest divided by the total number of recipients at risk.

[a]Death or graft failure and death were calculated via a modified Kaplan–Meier method.

[b]For graft failure, the Aalen–Johansen competing risk estimate is presented; death for causes not attributable to graft failure was the competing risk.

AZA, azathioprine; BOS, bronchiolitis obliterans syndrome; CI, confidence interval; CsA, cyclosporine A; IS, immunosuppression; MMF, mycophenolate mofetil; TAC, immediate-release tacrolimus.

TABLE 3.

Proportional hazard ratio estimates for time to death or graft failure based on maintenance immunosuppressive regimen at discharge

	TAC + MMF		TAC + AZA		CsA + MMF		CsA + AZA	
Model	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
With adjustment for covariates[a]	1	—	1.02 (0.90-1.16)	0.716	1.30 (1.09-1.56)	0.004	1.23 (1.04-1.46)	0.014
Without adjustment for covariates[b]	1	—	1.04 (0.92-1.17)	0.521	1.68 (1.43-1.98)	<0.001	1.35 (1.17-1.56)	<0.001
With adjustment for Tx time period[c]	1	—	0.94 (0.83-1.06)	0.324	1.43 (1.20-1.72)	<0.001	1.14 (0.97-1.34)	0.112

For all models, reference level is donated by 1.

[a]Multivariable proportional hazard model adjusting for age at transplant, recipient sex, lung transplant procedure, transplant time period, diagnosis, BMI, race, ethnicity, LAS at transplant, serum creatinine (mg/dL) at transplant, eGFR at transplant, total bilirubin (mg/dL) at transplant, length of hospital stay (days), donor age group, donor race, lung total ischemia time (hours), donor–recipient weight ratio, donor–recipient CMV matching, and induction with IL-2 receptor antagonists.

[b]Univariable proportional hazard model without adjustment for covariates.

[c]Multivariable proportional hazard model adjusting for time of transplantation (1999–2005, 2006–2009, and 2010–2017).

AZA, azathioprine; BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IL-2, interleukin-2, LAS, lung allocation score; MMF, mycophenolate mofetil; TAC, immediate-release tacrolimus; Tx, transplant.

to the relatively large proportion of lung transplant recipients in the CsA groups who had switched to TAC + MMF by 1 y posttransplant, as this crossover would be expected to lead to blunting of any differences between the groups.

Results of published randomized clinical trials comparing TAC- and CsA-based immunosuppressive regimens in adult lung transplant recipients are summarized in **Table S4, SDC**, http://links.lww.com/TP/C316.[8-12] These studies

TABLE 4.

Safety outcomes in adult lung transplant recipients by immunosuppressive regimen at hospital discharge

	TAC + MMF			TAC + AZA			CsA + MMF			CsA + AZA		
Outcome	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)	At risk, n	Events, n	Cumulative incidence (95% CI)
1 y posttransplant												
Hospitalization for infection	15 478	4055	26.2 (25.5, 26.9)	4263	1082	25.4 (24.1, 26.7)	1219	441	36.2 (33.5, 38.9)	1959	732	37.4 (35.2, 39.5)
NODAT	12 697	1909	15.0 (14.4, 15.7)	3642	854	23.4 (22.1, 24.8)	1055	156	14.8 (12.6, 16.9)	1782	264	14.8 (13.2, 16.5)
Renal dysfunction	15 478	1835	11.9 (11.3, 12.4)	4263	802	18.8 (17.6, 20.0)	1219	306	25.1 (22.7, 27.5)	1959	431	22.0 (20.2, 23.8)
Overall malignancy[a]	15 478	250	1.5 (1.3, 1.8)	4263	76	1.8 (1.4, 2.2)	1219	27	2.2 (1.5, 3.3)	1959	60	3.1 (2.4, 4.0)
PTLD[a]	15 478	114	0.7 (0.6, 0.8)	4263	35	0.8 (0.6, 1.1)	1219	16	1.3 (0.8, 2.2)	1959	42	2.2 (1.6, 2.9)
3 y posttransplant												
Hospitalization for infection	11 804	5504	46.6 (45.8, 47.4)	4019	1785	44.4 (42.9, 45.9)	1166	646	55.4 (52.6, 58.2)	1928	1083	56.2 (54.0, 58.4)
NODAT	9739	2161	22.2 (21.5, 22.9)	3454	1130	32.7 (31.2, 34.2)	1010	241	23.9 (21.3, 26.4)	1756	421	24.0 (22.0, 26.0)
Renal dysfunction	11 804	3026	25.6 (24.9, 26.3)	4019	1486	37.0 (35.5, 38.4)	1166	556	47.7 (44.9, 50.5)	1928	766	39.7 (37.6, 41.9)
Overall malignancy[a]	10 649	208	4.9 (4.4, 5.4)	3289	69	5.5 (4.8, 6.2)	857	24	5.8 (4.6, 7.3)	1463	31	6.2 (5.3, 7.4)
PTLD[a]	10 853	27	1.2 (1.0, 1.4)	3360	10	1.4 (1.1, 1.8)	876	7	2.2 (1.5, 3.2)	1485	9	3.0 (2.3, 3.8)

Unless otherwise stated, outcomes are expressed as percentages, calculated as the number of events over the time period of interest divided by the total number of recipients at risk. Individuals who were diabetic at transplant were not at risk for NODAT.

[a]For overall malignancy and PTLD, the Aalen–Johansen competing risk estimate is presented; death or graft failure is the competing risk. For year 1, the number at risk was all recipients; for year 3, the number at risk was the number at the earliest event in the year and the number of events was the total number of events over the year.

AZA, azathioprine; CI, confidence interval; CsA, cyclosporine A; MMF, mycophenolate mofetil; NODAT, new-onset diabetes after transplantation; PTLD, posttransplant lymphoproliferative disease; TAC, immediate-release tacrolimus.

did not report the incidence of the composite endpoint of graft failure and death, precluding direct comparison with the results of the present analysis. However, the observed rates of rejection at 1 y posttransplant (25.3% in the TAC + MMF group compared with 31.3%–49.4% in the other groups) are in line with the results of multicenter, prospective, randomized trials in lung transplant recipients showing rates of acute rejection at 1 y posttransplant to be numerically lower in TAC + MMF than CsA + MMF groups.[10-12]

In a prospective, randomized, multicenter study of MMF versus AZA in combination with CsA plus corticosteroids in 320 lung transplant recipients performed by McNeil et al,[19] no difference in acute rejection rate was seen between groups at 3 y posttransplant (56.6% with MMF versus 60.3% with AZA). Survival was 88% in the MMF group versus 80% in the AZA group at 1 y posttransplant ($P = 0.07$), and 75% in the MMF group compared to 69% in the AZA group at 3 y ($P = 0.18$). In another randomized trial comparing MMF versus AZA, both in combination with CsA and steroids, in 81 lung transplant recipients, Palmer et al[20] found no difference in the 6-mo acute rejection rate between groups (63% versus 58%, respectively; $P = 0.82$). The 6-mo survival rate was 86% with MMF versus 82% with AZA ($P = 0.57$).

Before 2002, immunosuppressive maintenance therapy following lung transplantation traditionally consisted of CsA and AZA, in combination with prednisone.[21] The main benefit of TAC and MMF as maintenance immunosuppression has been reported to be an improvement in any rejection, combined with advantages and/or differences in the adverse event profile and the ability to switch individuals with recurrent refractory rejection to more effective therapy.[21] Across the treatment regimens evaluated between 1999 and 2017 in the present study, the incidence of any rejection in adult lung transplant recipients at 1 y posttransplant was greatest in individuals treated with CsA + AZA (49.4%). The contribution of MMF for improving rejection prophylaxis compared with AZA was most evident when combined with CsA; the incidence of any rejection was 37.7% in the CsA + MMF group, corresponding to a relative reduction of 24% compared with CsA + AZA. However, the MMF treatment effect was also evident in the TAC-based groups. Although the overall incidence of any rejection at 1 y posttransplant was lower with the TAC-based regimens (31.3% for TAC + AZA versus 25.3% for TAC + MMF), the magnitude of the relative reduction was similar to that seen with the CsA-based regimens (ie, 19%).

The effect of tacrolimus as compared with CsA for improving rejection prophylaxis is evident both in combination with AZA (49.4% with CsA versus 31.3% with tacrolimus) and in combination with MMF (37.7% with CsA versus 25.3% with tacrolimus). As the lowest incidence

of any rejection (25.3%) and the lowest incidence of 1 y death or graft failure rate (8.6%) were observed following treatment with TAC + MMF, this regimen has become the standard of care in lung transplantation.

A major factor contributing to lung allograft dysfunction and failure beyond 1 y posttransplant is the increasing rate of BOS.[2,7,22,23] In this analysis, the incidence of BOS in the TAC + MMF group increased from 7.1% at 1 y posttransplant to 27.4% at 3 y. The cumulative incidence of BOS in the TAC + MMF group was similar to that seen in the other immunosuppressive regimen groups at both time points. In a previous prospective, randomized, multicenter trial, Zuckermann et al[12] found a similar incidence of BOS over 1 y of follow-up in lung transplant patients receiving TAC + MMF or CsA + MMF (8.1% [3/37] in both groups).

Factors found to be associated with a greater risk of graft failure or death in adult lung transplant patients receiving TAC + MMF in this analysis included older age (≥65 y), single-lung transplantation, longer hospital stay (>24 d), low body mass index (<18.5 kg/m^2), elevated serum creatinine (≥1.0 mg/dL), donor age ≥55 y, and donor race (black). These are known risk factors for lower survival after lung transplantation[5] and do not appear to represent unique risks associated with use of TAC + MMF, as the same baseline characteristics were also significantly associated with greater risk of graft failure or death in the CsA groups.

In this study, the incidence of all safety endpoints was similar or lower in the TAC + MMF group than in the other immunosuppression groups. The most commonly reported safety outcome in all groups was hospitalization for infection. It is well-documented that lung transplant recipients have a higher risk of infection and associated complications than other solid organ transplant populations.[24-26] Studies in other solid organ transplant populations have suggested a potentially increased risk of NODAT in individuals treated with TAC compared with CsA.[27] However, the incidence of NODAT in the TAC + MMF group in the present study was similar to or lower than that in the other immunosuppression groups. Although concerns have also been raised regarding the potential for nephrotoxicity in organ transplant recipients treated with calcineurin inhibitors,[6,28,29] we found rates of renal dysfunction to be lower in the TAC + MMF group than in the other immunosuppression groups at both 1 and 3 y posttransplant.

The main strengths of this analysis are the large lung transplant recipient population and the use of real-world evidence derived from the SRTR. Furthermore, the large number of lung transplant recipients included in the registry provides a high degree of precision for our estimates, as is evident from the narrow CIs. However, a number of potential limitations should be noted. Firstly, this was an observational study, and lung transplant recipients were not randomly assigned to immunosuppressive regimens. Exposure status in this study was based on intention to treat at discharge. Consequently, individuals that switch therapies during follow-up may diminish differences between exposure groups. Many factors may influence treatment decisions at discharge. Multivariable regression was used to attempt to account for differences between groups at baseline. Residual confounding may be present where modeling did not fully account for the effects of measured and unmeasured variables. We found TAC + MMF to have the highest continued use at 1 y posttransplant (72% and 35%–52% with other immunosuppressive regimens). Continued use of the discharge immunosuppressive regimen at 1 y posttransplant may provide a metric for assessing both safety and efficacy; if an individual does not tolerate the regimen and/or rejection cannot be controlled, there is likely to be a switch to an alternative therapy.

Second, data collection on index immunosuppressive regimen is collected at discharge in the registry, so it is not possible to observe the treatments received during transplant care before discharge. Left truncation was used to account for potential biases due to immortal time before discharge[30]; these estimates were consistent with sensitivity analyses indexing on discharge date. Thirdly, results of this study may not be generalizable to lung transplant recipient populations excluded from the study (eg, individuals undergoing retransplantation, multiorgan transplant recipients, and those who had previously received a solid organ transplant).

In addition, although the SRTR database provides reliable and complete data for death and graft failure in transplant recipients, reporting rates for secondary endpoints such as rejection, BOS, and safety outcomes may be less complete.[31,32] This is not expected to impact the comparison between immunosuppressive regimens but could potentially result in underestimation of the rates of these secondary endpoints. Data availability was considered relatively robust in this study. The proportion of lung transplant recipients in the TAC + MMF group with missing data was ≤5% for all secondary endpoints, except for BOS (8%–9%). However, the frequency of missing data was higher in the CsA + MMF group (up to 14.2%). A further limitation is that the analysis was limited to 1- and 3-y posttransplant outcomes.

The 21st Century Cures Act, which was signed into law in December 2016, created a provision for the FDA to develop frameworks for the use of real-world evidence to expand indications of approved medications.[33] This study formed the basis for one of the first uses of the SRTR database to provide real-world evidence to support the expansion of the product label for TAC (Prograf; Astellas Pharma, Inc.) to include lung transplantation.

In summary, use of TAC combined with MMF or AZA in lung transplant recipients at hospital discharge was associated with high graft and patient survival rates at 1 y posttransplant. TAC + MMF was associated with significantly lower rates of death or graft failure and numerically lower rates of rejection at 3 y posttransplant compared with CsA-based regimens, with no significant difference in the risk of graft failure or death seen between TAC + MMF and TAC + AZA. These findings support the use of TAC in combination with MMF or AZA as maintenance immunosuppressive regimens in adult lung transplant recipients.

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