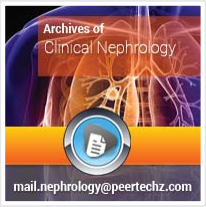
Peertechz



CLINICAL GROUP

ARCHIVES OF Clinical Nephrology OPEN ACCESS JOURNAL

ISSN: 2581-3870 DOI: https://dx.doi.org/10.17352/acn

Research Article

Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70

Amy H White*, John Hunton, Saleema Karim, Allison Wells, Hanna Jensen, Darby Derringer, Misha Karr, Sathyanand Kumaran and Lyle Burdine

University of Arkansas for Medical Sciences, Little Rock, AR, USA

Received: 08 February, 2023
Accepted: 15 February, 2023
Published: 16 February, 2023

***Corresponding author:** Amy H White, PharmD, BCPS, Pharmacy/Organ Transplant, University of Arkansas for Medical Sciences, 4301 W Markham St, Slot 571, Little Rock, AR 72205, USA, Tel: 1(501) 603-1631; Fax: 1(501) 686-6283; E-mail: awhite3@uams.edu

ORCiD: https://orcid.org/0000-0002-3950-1000

https://www.peertechzpublications.com

Check for updates

Abstract

Rates of kidney transplantation in patients over 70 years of age have steadily increased over the last 20 years, however age-appropriate immunosuppression regimens in the elderly remain unclear. Investigators utilized the SRTR database to evaluate elderly kidney transplant recipients' outcomes against a younger population.

Post-transplant outcomes measured at an approximately 1-year time interval included graft survival, patient survival, rejection, malignancy, and serum creatinine. Elderly patient survival was improved for those patients that were on dialysis for less than 1 year (95.4% *vs*. 91.4% $p < .01$). Patients able to be maintained on CNI immunosuppression regimens also had improved graft survival compared to those managed with other immunosuppression (95.5% *vs*. 91.1%, $p < .01$). Patients maintained on mTOR inhibitors had the lowest patient survival (85.5% *vs*. 92.6%, $p < .01$). The choice of induction therapy did not affect long term patient or graft survival. These results translated to investigators' own centers in patients over 60.

Results for the SRTR database showed that minimizing time on dialysis prior to transplant improved graft and patient survival, while the type of induction agent had minimal effect on all outcomes at the time of follow-up. The results also support the use of CNI's and belatacept for maintenance immunosuppression but did not encourage the use of mTOR inhibitors.

Introduction

Transplantation significantly decreases mortality compared to dialysis in the wait-listed elderly population with end-stage renal disease [1-3]. Although the number of elderly patients who undergo a kidney transplant is much lower compared to younger patients, transplant rates are increasing as the overall US population ages [4]. Elderly patients are much more likely to die waiting on a suitable allograft [4,5]. Importantly, once the transplant is initiated the elderly patient requires an individualized approach with respect to immune system modulation. Outcomes data for those patients that make it to transplant is limited to date [1,4,6,7].

Although post-transplant mortality is higher in elderly patients, there appears to be no consistent difference between outcomes in older and younger patients when graft survival data is censored for patient death [7-10]. Furthermore, there is clear evidence that elderly patients gain significant benefits from renal transplantation in terms of quality of life [7,8] However, a paucity of evidence exists to guide the different immunosuppressive strategies in the elderly since these patients are not often included in clinical trials evaluating

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

immunosuppressive drugs [11]. Given the already increased risk of infection and malignancy in the elderly [11], the appropriate choice of immunosuppressive agents is a critical component of the treatment plan [7,12].

Investigators sought to broadly evaluate the impact of several pretransplant factors and post-transplant immunosuppressive strategies on elderly transplant recipient outcomes using the nationwide Scientific Registry of Transplant Recipients (SRTR) database. Outcomes were then evaluated for elderly patients in the past four years at the investigator's single-institution transplant center to provide an additional frame of reference for the results.

Materials and methods

Data was collected from both a nationwide transplant registry (Scientific Registry of Transplant Recipients or SRTR) and the investigator's institutional kidney transplant population.

The United States SRTR database was utilized to capture kidney transplant recipients in the United States between June 1994 and August 2017. Patients were divided into elderly (70 years of age or older), and non-elderly (69 years of age or younger). Any patients who received dual organ transplants with other organs were excluded. Post-transplant outcomes were measured at various times in the SRTR database based on available data. The follow-up time period was around 1-year post-transplant in a majority of patients.

Investigators then analyzed the institutional population of older patients who received a kidney transplant at the University of Arkansas for Medical Sciences (UAMS) between July 2015 and August 2019. To increase the number of patients to analyze, the elderly was defined as 60 years and older in this cohort. Any patients who received multiorgan transplants with other organs were excluded. Post-transplant outcomes were measured at the 1-year time interval.

Recipient demographics such as age, gender, race and blood type were compared between the different study groups in order to assess differences at the population level.

The post-transplant outcomes of interest in both cohorts included: graft survival, patient survival, rejection, malignancy, and serum creatinine.

In addition, donor and recipient characteristics such as Donation after Brainstem Death (DBD), Donation after Circulatory Death (DCD), time on dialysis prior to transplant, and Cold Ischemia Time (CIT) were analyzed in both cohorts for impact on transplant outcomes. The Kidney Donor Profile Index (KDPI) impact on transplant outcomes in the UAMS population was analyzed but this data was unavailable in the SRTR cohort.

Potential significant associations between selected donor or recipient characteristics, immunosuppression strategies, and post-transplant outcomes of interest were assessed using two-sample t-tests for continuous variables and Pearson chi-square tests for categorical variables. For the SRTR dataset transplant outcomes and demographics were compared between the elderly and non-elderly patients using t-tests and chi-square tests as well. The data management and analyses were performed using STATA [17.0] and R version [4.1.0].

This study was approved by the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board (IRB260995).

Results

SRTR

The total number of study participants in the SRTR included 172,350 patients. Kidney transplant recipients ranged from 40 to 96 years of age. There were 12,096 patients in the elderly group and 160,252 patients in the non-elderly group. The average age in the elderly group was 73 years old while the non-elderly group had an average age of 54 years old. A majority of recipients in both the elderly and non-elderly patient groups were white males who had been on dialysis for an average of 3.5 years prior to the transplant. Elderly patients were more likely to receive kidneys from older, extended-criteria donors than non-elderly patients (Table 1). On average, a patient's follow-up period was documented 346 days after their kidney transplant.

UAMS

The UAMS cohort examined 105 elderly kidney transplant recipients. Patients ranged from 60 to 78 years of age. Twenty-six of the patients were over the age of 70. A majority of patients were white males, but this population did have a higher percentage of black patients at 34.3% compared to 18.5% in the SRTR elderly group. The UAMS elderly population had a higher percentage of patients receiving preemptive transplants (20% *vs.* 12.2%) and higher average cold ischemia times (27.3 hours *vs.* 18.9 hours) (Table 1).

Patient/Transplant factors

In the SRTR cohort, preemptive transplants had significantly higher graft and patient survival (97.4% and 96.2%) than patients who were on dialysis prior to the transplant (94.9% and 91.7%). Patients on dialysis for less than 1 year also had improved survival rates compared to patients who required dialysis longer than 1 year (95.4% *vs.* 91.4%). The UAMS cohort did not quantify any significant differences in dialysis time (Table 2).

When compared to the SRTR younger population, elderly patients had higher rates of graft survival when they were able to receive a preemptive transplant (97.4% *vs.* 96.3%) or had only been on dialysis less than one year prior to the transplant (96.7% *vs.* 95.6%). Mortality increased in the elderly when they received a transplant after starting dialysis (8.3% *vs.* 4.4%) while preemptive transplants had no difference in patient survival across age groups (Table 3).

Neither utilizing donors after cardiac deaths nor grafts with prolonged cold ischemia significantly impacted graft survival or median serum creatinine in the elderly at the time of follow-up (Table 2).

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

Table 1: Demographics.

Variable	SRTR < 70 years old	SRTR > 70 years old	*p* - value	UAMS
Recipient Demographics				
Age (years), mean ± SD	54 ± 8.1	73 ± 2.9	< 0.01	66.37 ± 4.60
Male gender, n (%)	97,944 (61.1%)	7,926 (65.5%)	< 0.01	59 (56.19%)
Race White, n (%) Black, n (%) Asian, n (%)	 100,665 (62.8%) 48,255 (30.1%) 8,562 (5.34%)	 8,977 (74.2%) 2,241 (18.5%) 732 (6.1%)	< 0.01	 63 (60%) 36 (34.3%) 2 (1.9%)
Recipient Blood Type O, n (%) A, n (%) B, n (%) AB, n (%)	 71,178 (44.4%) 60, 524 (37.8%) 20,216 (12.6%) 8,331 (5.2%)	 5,191 (42.9%) 4,805 (40%) 1,453 (12%) 647 (5.4%)	< 0.01	Not collected
Preemptive transplant, n (%)	15,383 (9.6%)	1,478 (12.2%)	< 0.01	21 (20%)
Time on Dialysis (months), mean ± SD	1282 ± 1032	1282 ± 1215	< 0.01	Unable to be collected
Previous Transplant(s), n (%)	19,288 (12.1%)	12,093 (5.9%)	< 0.01	4 (3.8%)
Donor Demographics				
Age (years), mean ± SD	37.5 ± 16.7	45.7 ± 17.2	< 0.01	40.4 ± 12
Male Gender n (%)	96,118 (60%)	6,798 (56.2%)	< 0.01	Not collected
Race White, n (%) Black, n (%) Asian, n (%)	 135,758 (84.8%) 19,914 (12.4%) 3,213 (2%)	 10,254 (84.8%) 1,427 (11.8%) 289 (2.4%)	< 0.01	Not collected
Blood Type O, n (%) A, n (%) B, n (%) AB, n (%)	 75,255 (47%) 62,447 (39%) 18,658 (11.6%) 3,888 (2.4%)	 5,460 (45%) 5,076 (42%) 1,333 (11%) 227 (1.9%)	< 0.01	Not collected
DCD donors, n (%)	14,225 (10.4%)	1,376 (11.7%)	< 0.01	24 (22.9%)
ECD donor, n (%)	24,814 (15.5%)	4,451 (36.8%)	< 0.01	Not collected
Transplant				
Total Cold Ischemia Time (Hours), mean ± SD	19.5 ± 9.4	18.9 ± 9.4	< 0.01	27.3 ± 10.3
Immunosuppression				
Lymphocyte Depleting Induction, n (%)	74,791 (74.5%)	5,526 (67%)	< 0.001	56 (53.3%)
Calcineurin inhibitor, n (%)	151,259 (95.6%)	10,765 (92.3%)	0.95	97 (92.4%)
Belatacept, n (%)	778 (0.5%)	114 (1%)	< 0.001	13 (12.4%)
mTOR inhibitor, n (%)	7912 (5%)	448 (3.9%)	< 0.001	8 (7.6%)

DCD: Donation after Circulatory Death; ECD: Expanded Criteria Donor; mTOR: mammalian Target of Rapamycin.

In the UAMS cohort, graft survival was similar in both patients who received kidneys from donors with a KDPI of less than 70% and over 70% (96% *vs.* 93.1%). The mean serum creatinine was also similar in both groups at 1.53 mg/dL in kidneys with KDPI less than 70% and 1.75 mg/dL in kidneys with KDPI over 70% (Table 2).

Induction immunosuppression

Patients were evaluated on whether they received induction immunosuppression with lymphocyte-depleting therapy (anti-thymocyte globulin, alemtuzumab, or OKT3) or non-lymphocyte-depleting therapy (basiliximab).

The type of induction agent had no significant effect on any outcome at the time of follow-up in either cohort. The elderly population found no difference in graft survival, patient survival, median SCr, malignancy, or rejection (Table 2).

Maintenance immunosuppression

The SRTR findings support the common use of Calcineurin Inhibitors (CNIs) in the elderly population. Over 95% of patients in both cohorts were reported to have utilized a CNI as part of their maintenance immunosuppression regimen. In the SRTR cohort, CNI-containing regimens were associated with a significant improvement in graft survival (95.5% *vs.* 91.1%), lower serum creatinine levels (1.3 *vs.* 1.4 mg/dL), and lower rates of rejection (9.3% *vs.* 16.2%) compared with elderly recipients with maintenance immunosuppression that did not contain a CNI. No differences in patient survival or malignancy were observed (Table 2).

114 elderly patients in the SRTR cohort were reported to have been on belatacept as maintenance immunosuppression during their follow-up period. There was no difference in graft survival, patient survival, serum creatinine, or

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

Table 2: SRTR and UAMS Elderly transplant outcomes.

	SRTR (*n* = 12,096)		*P* value	UAMS (*n* = 105)		*P* value
Patient/Transplant factors						
	Preemptive TXP	**Dialysis prior to TXP**		**Preemptive TXP**	**Dialysis prior to TXP**	
Graft survival, n (%)	1,401 (97.4%)	9,742 (94.9%)	< 0.001	20 (95.2%)	80 (95.2%)	> 0.999
Patient survival, n (%)	1,380 (96.2%)	9,385 (91.7%)	< 0.001	20 (95.2%)	81 (96.4%)	> 0.999
	Dialysis < 1 year	Dialysis > 1 year		Dialysis < 1 year	Dialysis > 1 year	
Graft survival, n (%)	2,585 (96.9%)	8,558 (94.7%)	< 0.001	29 (90.6%)	71 (97.3%)	0.331
Patient survival, n (%)	2,537 (95.4%)	8,228 (91.4%)	< 0.001	29 (90.6%)	72 (98.6%)	0.156
	DBD	DCD		DBD	DCD	
Graft survival, n (%)	9,556 (95.4%)	1,267 (95.8%)	0.57	76 (96.2%)	22 (91.7%)	0.716
SCr, mean ± SD	1.45 ± 0.67	1.47 ± 0.67	0.2	1.55 ± 0.77	1.69 ± 1.15	0.501
	KDPI < 70%	KDPI > 70%		KDPI < 70%	KDPI > 70%	
Graft survival, n (%)				72 (96%)	27 (93.1%)	0.914
SCr, mean ± SD				1.53 ± 0.88	1.75 ± 0.82	0.257
	CIT < 24h	CIT > 24h		CIT < 24h	CIT > 24h	
Graft survival, n (%)	8,488 (95.7%)	2,655 (93.7%)	0.09	37 (94.9%)	63 (95.5%)	> 0.999
SCr, mean ± SD	1.43 ± 0.64	1.54 ± 0.71	0.16	1.57 ± 0.96	1.59 ± 0.8	0.895
Induction Immunosuppression						
	Lymphocyte depleting induction	Non Lymphocyte Depleting induction		Lymphocyte depleting induction	Non Lymphocyte Depleting induction	
Graft survival, n (%)	5,269 (95.4%)	2,620 (96.2%)	0.09	55 (98.2%)	45 (91.8%)	0.284
Patient survival, n (%)	5,117 (92.9%)	2,516 (96.2%)	0.76	56 (100%)	45 (91.8%)	0.095
SCr, mean ± SD	1.45 ± 0.66	1.43 ± 0.64	0.23	1.59 ± 0.78	1.58 ± 0.96	0.958
Malignancy, n (%)	144 (2.8%)	75 (2.9%)	0.83			
Rejection, n (%)	33 (8.6%)	19 (5.8%)	0.2	7 (12.5%)	7 (14.3%)	> 0.999
	SRTR (*n* = 12,096)		P value	UAMS (*n* = 105)		P value
Maintenance Immunosuppression						
	CNI	Other IMS		CNI	Other IMS	
Graft survival, n (%)	10,514 (95.5%)	461 (91.1%)	< 0.001	92 (94.8%)	8 (100%)	> 0.999
Patient survival, n (%)	10,140 (92.4%)	457 (90.9%)	0.23	93 (95.9%)	8 (100%)	> 0.999
SCr, mean ± SD	1.45 ± 0.66	1.53 ± 0.73	0.01	1.58 ± 0.89	1.64 ± 0.41	0.855
Malignancy, n (%)	260 (2.6%)	11 (2.5%)	0.99			
Rejection, n (%)	184 (9.3%)	18 (16.2%)	0.03	12 (12.4%)	2 (25%)	0.639
	Belatacept	Other IMS		Belatacept	Other IMS	
Graft survival, n (%)	109 (95.6%)	10,866 (95.3%)	0.99	3 (100%)	97 (95.1%)	> 0.999
Patient survival, n (%)	104 (91.2%)	10,493 (92.4%)	0.79	3 (100%)	98 (96.1%)	> 0.999
SCr, mean ± SD	1.37 ± 0.52	1.46 ± 0.66	0.18	1.47 ± 0.25	1.59 ± 0.87	0.812
Malignancy, n (%)	4 (3.6%)	267 (2.6%)	0.73			
Rejection, n (%)	No results reported in SRTR			0 (0%)	14(13.7%)	> 0.999
	mTOR	Other IMS		mTOR	Other IMS	
Graft survival, n (%)	411 (91.7%)	10,564 (95.5%)	< 0.001	7 (87.5%)	93 (95.9%)	0.837
Patient survival, n (%)	379 (85.4%)	10,218 (92.6%)	< 0.001	7 (87.5%)	94 (96.9%)	0.708
SCr, mean ± SD	1.7 ± 0.78	1.45 ± 0.66	< 0.001	2.89 ± 2.1	1.49 ± 0.61	< 0.001
Malignancy, n (%)	11 (2.7%)	260 (2.6%)	0.99			
Rejection, n (%)	10 (6.3%)	192 (10%)	0.18	1 (12.5%)	13 (13.4%)	> 0.999

SRTR : Scientific Registry of Transplant Recipients ; TXP : Transplant ; DCD: Donation after Circulatory Death; DBD: Donation after Brainstem Death; KDPI: Kidney Donor Profile Index ; CIT: Cold Ischemia Time; IMS: Immunosuppression ; mTOR : mammalian Target of Rapamycin

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

Table 3: SRTR Elderly and Non-elderly outcomes.

	SRTR < 70 years old	SRTR > 70 years old	*P* value
Patient/Transplant factors			
Preemptive txp graft survival, n (%) On dialysis prior to txp graft survival, n (%)	14,788 (96.3%) 137,427 (95%)	1,439 (97.4%) 10,065 (94.9%)	0.039 0.6
Preemptive txp patient survival, n (%) On dialysis prior to txp patient survival, n (%)	14,811 (96.3%) 137,855 (95.2%)	1,416 (95.8%) 9,695 (91.3%)	0.069 < 0.001
Dialysis < 1 year graft survival, n (%) Dialysis > 1 year graft survival, n (%)	32,319 (95.6%) 119,896 (95%)	2,644 (96.8%) 8,860 (94.7%)	0.003 0.218
Dialysis < 1 year patient survival, n (%) Dialysis > 1 year patient survival, n (%)	32,530 (96%) 120,136 (95.1%)	2,594 (94.9%) 8,517 (91%)	< 0.001 < 0.001
DBD graft survival, n (%) DCD graft survival, n (%)	117,991 (96.2%) 13,720 (96.5%)	9,865 (95.3%) 1,319 (95.9%)	< 0.001 0.260
DBD SCr, mean ± SD DCD SCr, mean ǀ SD	1.52 ± 0.72 1.52 ± 0.7	1.45 ± 0.66 1.47 ± 0.66	< 0.001 0.025
CIT < 24h graft survival, n (%) CIT > 24h graft survival, n (%)	111,339 (95.7%) 40,876 (93.6%)	8,695 (95.7%) 2,809 (93.5%)	0.871 0.884
CIT < 24h SCr, mean ± SD CIT > 24h SCr, mean ± SD	1.52 ± 0.7 1.64 ± 0.8	1.43 ± 0.64 1.54 ± 0.71	< 0.001 < 0.001
Induction Immunosuppression			
LD graft survival, n (%) ND graft survival, n (%)	71,902 (96.2%) 21,931 (96.6%)	5,630 (95.3%) 2,981 (95.9%)	0.001 0.049
LD patient survival, n (%) ND patient survival, n (%)	71,810 (96%) 21,665 (95.4%)	5,463 (92.4%) 2,862 (92.1%)	< 0.001 < 0.001
LD SCr, mean ± SD ND SCr, mean ± SD	1.5 ± 0.7 1.48 ± 0.68	1.44 ± 0.65 1.43 ± 0.63	< 0.001 < 0.001
LD malignancy, n (%) ND malignancy, n (%)	722 (1%) 244 (1.1%)	148 (2.5%) 79 (2.6%)	< 0.001 < 0.001
LD rejection, n (%) ND rejection, n (%)	2,033 (13.7%) 351 (5.9%)	33 (7.9%) 19 (5.2%)	0.001 0.175
Maintenance Immunosuppression			
CNI graft survival, n (%) Other IMS graft survival, n (%)	144,391 (95.6%) 6,151 (89%)	10,862 (95.5%) 474 (90.5%)	0.745 0.291
CNI patient survival, n (%) Other IMS patient survival, n (%)	144,405 (95.5%) 6,397 (92.4%)	10,471 (92%) 472 (90.1%)	< 0.001 0.083
CNI SCr, mean ± SD Other IMS SCr, mean ± SD	1.54 ± 0.7 1.66 ± 0.9	1.45 ± 0.7 1.52 ± 0.7	< 0.001 0.0017
CNI malignancy, n (%) Other IMS malignancy, n (%)	1,225 (1%) 52 (0.9%)	264 (2.5%) 11 (2.2%)	< 0.001 0.012
CNI rejection, n (%) Other IMS rejection, n (%)	7,884 (12.4%) 586 (18.2%)	184 (8.6%) 18 (14.9%)	< 0.001 0.141
Belatacept graft survival, n (%) Other IMS graft survival, n (%)	762 (97.9%) 149,780 (95.3%)	114 (95.8%) 11,222 (95.3%)	0.15 0.962
Belatacept patient survival, n (%) Other IMS patient survival, n (%)	712 (96.3%) 146,992 (95.8%)	104 (91.2%) 10,493 (92.4%)	0.022 < 0.001
Belatacept SCr, mean ± SD Other IMS SCr, mean ± SD	1.39 ± 0.6 1.55 ± 0.7	1.37 ± 0.5 1.46 ± 0.7	0.754 < 0.001
Belatacept malignancy, n (%) Other IMS malignancy, n (%)	5 (0.7%) 1,272 (1%)	4 (3.4%) 271 (2.4%)	0.022 < 0.001
Belatacept rejection, n (%) Other IMS rejection, n (%)	No results reported		
mTOR graft survival, n (%) Other IMS graft survival, n (%)	7,481 (94.6%) 143,061 (95.3%)	415 (91.2%) 10,921 (95.5%)	0.003 0.538
mTOR patient survival, n (%) Other IMS patient survival, n (%)	7,451 (94.2%) 143,351 (95.4%)	385 (84.6%) 10,558 (92.2%)	< 0.001 < 0.001
mTOR SCr, mean ± SD Other IMS SCr, mean ± SD	1.7 ± 0.9 1.54 ± 0.7	1.7 ± 0.8 1.45 ± 0.7	0.88 < 0.001
mTOR malignancy, n (%) Other IMS malignancy, n (%)	55 (0.7%) 1,222 (1%)	11 (2.4%) 264 (2.4%)	< 0.001 < 0.001
mTOR rejection, n (%) Other IMS rejection, n (%)	256 (7.4%) 8,214 (13%)	10 (5.9%) 192 (9.2%)	0.696 < 0.001

DBD: Donation after Brain Death; DCD: Donation after Circulatory Death; CIT: Cold Ischemia Time; LD: Lymphocyte depleting; ND: Non-lymphocyte Depleting; CNI: Calcineurin Inhibitor; IMS: Immunosuppression; mTOR: mammalian Target of Rapamycin

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

malignancy with belatacept in comparison to patients on other immunosuppressive agents. Rejection rates were unable to be evaluated as none of the 114 patients had follow-up data regarding rejection (Table 2).

The use of a Mammalian Target of Rapamycin (mTOR) inhibitor in a maintenance immunosuppression regimen was not found to be associated with favorable outcomes in the elderly population. The SRTR cohort found that mTOR inhibitors were associated with lower rates of working grafts (91.7% *vs.* 95.5%), significantly decreased patient survival (85.4% *vs.* 92.6%) and higher serum creatinine levels (1.5 *vs.* 1.3 mg/dL). There were no differences in malignancy or rejection rates (Table 2).

There was no significant difference in outcomes in the UAMS cohort among the CNI and belatacept groups but found a significantly higher serum creatinine at 1 year post-transplant for elderly patients on an mTOR inhibitor compared with those on other immunosuppression regimens (2.89 mg/dL *vs.* 1.49 mg/dL) (Table 2).

When comparing maintenance immunosuppression regimens in the SRTR elderly and nonelderly populations, higher rates of malignancy were seen across all immunosuppression regimens (2.4% - 3.4% in the elderly group *vs.* 0.7%-1% in the nonelderly). Graft survival rates were similar across all regimens except for mTOR inhibitors being associated with decreased graft survival in the elderly population (95.5% in other immunosuppression regimens *vs.* 91.7% with mTOR inhibitor therapy). Rejection rates were lower in elderly patients receiving an immunosuppression regimen containing a CNI (9.3% *vs.* 16.2%) (Table 3).

Discussion

This study found elderly transplant recipients have high rates of graft survival rivaling their younger counterparts. Investigation of the SRTR dataset revealed that time on dialysis prior to transplant in the elderly should be minimized for the most favorable outcomes post-transplant. Interestingly, the choice of induction agent did not seem to affect outcomes. Elderly patients treated with a lymphocyte-depleting agent were not at increased risk of malignancy or infections compared to those who received non-depleting induction. Likewise, neither graft cold ischemia times nor whether the graft was from a brain-dead donor or deceased cardiac donor affected outcomes. Both SRTR and UAMS cohorts found less favorable outcomes when a patient's post-transplant immunosuppression regimen contained an mTOR inhibitor.

These results challenge the paradigm that elderly patients are less suitable for transplantation. Naturally, several intrinsic factors must be considered regarding kidney transplants in the elderly. The effector immune response declines in magnitude with age, however, this advantage with respect to transplantation may be offset by the increased vulnerability to infection and malignancy [13,14]. Urinary Tract Infections (UTIs) are the most common infections post-transplant and are proven to increase the risk for post-transplant mortality. Older age is a significant risk factor in the development of UTIs, despite not proving to be associated with higher rates of ureteral stent colonization, elderly patients may require more anti-infective medications to prevent recurrent UTIs (Chuang P, Sarier) [15,16]. In addition, the pharmacokinetics including absorption, distribution, and metabolism of drugs are different in this population compared to younger patients [17]. Lower albumin levels in the elderly lead to increased unbound free concentration of medications, such as calcineurin inhibitors, and ultimately increased exposure to medications despite therapeutic targets, similar to the phenomenon seen in pregnancy post-transplant [18]. A decrease in liver functional reserve, a higher prevalence of comorbid conditions, and drug-drug interactions have a significant impact on the tolerability of immunosuppressive medications [7]. Importantly, older patients tend to get allocated deceased donor kidneys from expanded criteria donors, cardiac death donors, or grafts with prolonged cold ischemic time [7,11]. These factors can perhaps have negatively affected the post-transplant outcomes in the elderly [7].

Although not statistically significant, investigators were surprised to find a slightly higher percentage of rejection in patients receiving lymphocyte-depleting induction in both age groups. This may indicate transplant teams are good at identifying low-risk populations to administer non-depleting induction immunosuppression strategies, or that lymphocyte-depleting agents cause side effects such as infection or neutropenia leading to fluctuating dosing of maintenance immunosuppression regimens. More investigation into the causes of higher rejection rates is warranted.

The use of mTOR inhibitors in the elderly population and its association with less favorable long-term outcomes was also found in a previous SRTR database analysis by Santos and colleagues [17]. Santos found immunosuppression regimens that included sirolimus in combination with tacrolimus or mycophenolate in patients over the age of 65 led to the decreased patient and graft survival in comparison with tacrolimus, mycophenolate, prednisone regimens. Interestingly it was previously shown by McTaggart, et al. that sirolimus prolongs delayed graft function and is also not recommended in the early phase of transplantation [19]. This result could be a consequence of selection bias if these patients were transitioned to an mTOR-based regimen due to an inability to tolerate a CNI-based immunosuppression regimen.

Evaluating transplant recipients from the SRTR database has a major limitation in the amount of missing data points throughout the dataset. Investigators are not able to distinguish if these missing data points would affect outcomes. Another limitation is the lack of dosing information for immunosuppression. Many organ transplant centers do one of the most utilized lymphocyte-depleting induction agents, thyroglobulin, differently and may adjust dosages based on the transplant recipient risk profile. The dataset is also not set up to evaluate dosing or goal levels for maintenance immunosuppression agents. These factors play a major role in determining a recipient's risk of graft loss, rejection, infections, etc which ultimately could have affected the findings of this study.

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063

The number of elderly patients receiving renal transplant has progressively increased over the past 30 years [1,4] and since 2000, the number of deceased-donor transplants in this population have doubled [4]. In the United States, renal transplants performed in patients over the age of 65 years have increased by 50% from 2010 to 2019, with the absolute number of patients in this age category who received kidney transplants being 5,129 in 2019 *vs*. 2,814 in 2010 [20]. This study shows encouraging results to accompany this trend.

Overall, transplanting elderly patients has similar 1-year graft outcomes compared with younger patient populations. Elderly transplant recipients have the best outcomes when dialysis time prior to transplant is minimized, and they do not require mTOR inhibitor immunosuppression. Type of donor death, cold ischemia time and induction agent utilized have minimal effect on 1-year outcomes. The data may provide valuable guidance to transplant centers when considering cardiac death donors and kidneys with long cold ischemia times in elderly transplant recipients. Based on this research, investigators highly recommend that post-transplant immunosuppression regimens in the elderly contain a CNI unless there is an absolute contraindication.

Data availability

The data that support the SRTR findings of this study are available from SRTR. The data that support the findings of the UAMS study are available from the corresponding author upon reasonable request.

References

1. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. Transplantation. 2007 Apr 27;83(8):1069-74. doi: 10.1097/01.tp.0000259621.56861.31. PMID: 17452897.

2. Oniscu GC, Brown H, Forsythe JL. How great is the survival advantage of transplantation over dialysis in elderly patients? Nephrol Dial Transplant. 2004 Apr;19(4):945-51. doi: 10.1093/ndt/gfh022. PMID: 15031354.

3. Johnson DW, Herzig K, Purdie D, Brown AM, Rigby RJ, Nicol DL, Hawley CM. A comparison of the effects of dialysis and renal transplantation on the survival of older uremic patients. Transplantation. 2000 Mar 15;69(5):794-9. doi: 10.1097/00007890-200003150-00020. PMID: 10755528.

4. Faravardeh A, Eickhoff M, Jackson S, Spong R, Kukla A, Issa N, Matas AJ, Ibrahim HN. Predictors of graft failure and death in elderly kidney transplant recipients. Transplantation. 2013 Dec 27;96(12):1089-96. doi: 10.1097/TP.0b013e3182a688e5. PMID: 24056622.

5. Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche HU. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. Clin J Am Soc Nephrol. 2009 Jul;4(7):1239-45. doi: 10.2215/CJN.01280209. Epub 2009 Jun 18. PMID: 19541814; PMCID: PMC2709520.

6. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999 Dec 2;341(23):1725-30. doi: 10.1056/NEJM199912023412303. PMID: 10580071.

7. Danovitch G, Savransky E. Challenges in the counseling and management of older kidney transplant candidates. Am J Kidney Dis. 2006 Apr;47(4 Suppl 2):S86-97. doi: 10.1053/j.ajkd.2005.12.042. PMID: 16567243.

8. Fabrizii V, Winkelmayer WC, Klauser R, Kletzmayr J, Säemann MD, Steininger R, Kramar R, Hörl WH, Kovarik J. Patient and graft survival in older kidney transplant recipients: does age matter? J Am Soc Nephrol. 2004 Apr;15(4):1052-60. doi: 10.1097/01.asn.0000120370.35927.40. PMID: 15034109.

9. Doyle SE, Matas AJ, Gillingham K, Rosenberg ME. Predicting clinical outcome in the elderly renal transplant recipient. Kidney Int. 2000 May;57(5):2144-50. doi: 10.1046/j.1523-1755.2000.00066.x. PMID: 10792636.

10. Oniscu GC, Brown H, Forsythe JL. How old is old for transplantation? Am J Transplant. 2004 Dec;4(12):2067-74. doi: 10.1111/j.1600-6143.2004.00622.x. PMID: 15575911.

11. Montero N, Pérez-Sáez MJ, Pascual J; DESCARTES Working Group; DESCARTES ERA-EDTA Board:; Abramowicz D, Budde K, Dudley C, Hazzan M, Klinger M, Maggiore U, Oberbauer R, Pascual J, Sorensen SS, Viklicky O. Immunosuppression in the elderly renal allograft recipient: a systematic review. Transplant Rev (Orlando). 2016 Jul;30(3):144-53. doi: 10.1016/j.trre.2016.05.001. Epub 2016 May 20. PMID: 27279024.

12. Martins PN, Pratschke J, Pascher A, Fritsche L, Frei U, Neuhaus P, Tullius SG. Age and immune response in organ transplantation. Transplantation. 2005 Jan 27;79(2):127-32. doi: 10.1097/01.tp.0000146258.79425.04. PMID: 15665758.

13. Knoll GA. Kidney transplantation in the older adult. Am J Kidney Dis. 2013 May;61(5):790-7. doi: 10.1053/j.ajkd.2012.08.049. Epub 2012 Dec 20. PMID: 23261121.

14. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67-76. doi: 10.1080/03602530902722679. PMID: 19514965.

15. Chuang P, Parikh CR, Langone A. Urinary tract infections after renal transplantation: a retrospective review at two US transplant centers. Clin Transplant. 2005 Apr;19(2):230-5. doi: 10.1111/j.1399-0012.2005.00327.x. PMID: 15740560.

16. Sarier M, Demir M, Duman I, Yuksel Y, Demirbas A. Evaluation of Ureteral Stent Colonization in Live-Donor Renal Transplant Recipients. Transplant Proc. 2017 Apr;49(3):415-419. doi: 10.1016/j.transproceed.2017.01.004. PMID: 28340803.

17. Yuksel Y, Yuksel D, Yucetin L, Erbis H, Sarier M, Karatas O, Emek M, Erdogan M, Yavuz A, Demirbas A. Use of Tacrolimus During Pregnancy After Kidney Transplantaion. Transplant Proc. 2019 Sep;51(7):2361-2366. doi: 10.1016/j.transproceed.2019.01.150. Epub 2019 Aug 8. PMID: 31402247.

18. Santos AH Jr, Chen C, Alquadan K, Wen X. Outcomes of sirolimus regimens in 65-year-old and older kidney transplant recipients: a registry-based observational study. Int Urol Nephrol. 2019 Nov;51(11):2063-2072. doi: 10.1007/s11255-019-02251-w. Epub 2019 Aug 5. PMID: 31385180.

19. McTaggart RA, Gottlieb D, Brooks J, Bacchetti P, Roberts JP, Tomlanovich S, Feng S. Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am J Transplant. 2003 Apr;3(4):416-23. doi: 10.1034/j.1600-6143.2003.00078.x. PMID: 12694063.

20. Organ Procurement and Transplantation Network. Health Resources and Services Administration, U.S. Department of Health & Human Services. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3087785/.

Citation: White AH, Hunton J, Karim S, Wells A, Jensen H, et al. (2023) Analysis of induction and maintenance immunosuppression choices in the US during the first year post kidney transplant for patients over 70. Arch Clin Nephrol 9(1): 001-007. DOI: https://dx.doi.org/10.17352/acn.000063